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STUDIES ON THE CONCENTRATIONS OF ESTROGENIC AND GONADOTROPIC HORMONES IN THE SERUM OF PREGNANT WOMEN*

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THE significance of the manifold changes in the sex hormones which occur during pregnancy remains largely an enigma, chiefly because of the complexity of the hormonal variations, the difficulties attendant upon their quantitative estimation, and an incomplete knowledge of their metabolism. Nevertheless, the scant information which has been derived from even the crude methods of study available has proved to be of considerable value, as for example in the establishment of a diagnosis of pregnancy, presumptive evidence of fetal death, or the presence of tumors arising from chorionic tissue.

Increasing evidence that a number of other complications and abnormalities of pregnancy are associated with, if not actually related etiologically to, variations in the concentrations of the sex hormones, has lent clinical significance to the quantitative estimation of these substances in the body fluids and tissues of the gravid woman.

Unfortunately, however, many such studies are based on rather scant laboratory data. Indeed studies of the sex hormone values in normal pregnancy are surprisingly few. Furthermore such scant data are hardly applicable to general use, since it is well known that discrepancies in biologic titrations obtained in different laboratories are often so great, owing to differences in test animals, technique and interpretation, as to make comparative results unreliable. It is desirable therefore for each obstetric laboratory engaging in hormonal titrations to establish for itself a set of normal values based on a standardized technique.

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This study concerns itself with a simplified improved technique for the titration of estrogenic and gonadotropic hormones in the serum of pregnant women, which proved to be useful in following the concentrations of these hormones in normal gestation, together with similar studies in a number of the complications of pregnancy, especially in the toxemias and abortion.

METHODS

Early in this study determinations of the estrogenic and gonadotropic hormones were made in both the urine and serum of pregnant women. Preliminary studies made at daily intervals soon revealed that much more constant results were obtained from the blood serum than from twenty-four-hour urine specimens, although the values followed each other in a rough fashion. This was probably the result of a number of factors, including errors inherent in the extraction of the hormones from the urine, the presence of the hormones in several conjugated forms in the urine, difficulty in obtaining accurate twenty-four-hour outputs in ambulatory patients, and perhaps variations due to a mechanism regulating the concentration in the tissues. It was felt that titrations of the blood serum were much more likely to be applicable for routine clinical use, and that the information obtained would be of greater significance than urinary titrations, although it must be admitted that the latter furnishes information of additional value.

Although some studies have been reported on the concentration of estrogenic and gonadotropic substances in whole blood and serum during pregnancy, their number and accuracy have been limited by the large quantities of blood which were necessary for the biologic tests employed. This difficulty was apparently the result of the loss of most of the hormone by extraction methods, and the use of rats rather than mice as test animals, thus requiring larger amounts of serum and permitting the use of fewer animals.

By using the unextracted sera as the test solutions and mice as the test animals a simplified technique for biologic titrations was developed by which reliable results are obtainable with from 20 to 50 c.c. of blood, depending upon the period of gestation.

Estrogenic Hormone.—A modification of Fluhmann's technique[2] was employed. The test animals were young, adult, castrated mice of about eight weeks of age and 25 gm. in weight, which were used exactly seven days after castration. Atrophy of the vaginal wall was confirmed by examining smears for two days before use. Whole or diluted serum was injected subcutaneously in 6 divided doses over a period of three days. The animals were sacrificed on the fourth afternoon and biopsies were taken from the middle portion of the vagina. Histologic sections were prepared by a rapid technique and stained with hematoxylin and eosin. The least amount of serum which produced complete hyperplasia to vaginal cornification (Reactions 4 to 5, Fluhmann) was regarded as containing one mouse unit. Also the uterine cornua were examined macroscopically for estrus, since with this technique macroscopically positive uteri indicated dosages several times the amount necessary to produce vaginal cornification.

For the initial titration 3 to 6 animals were injected with varying amounts of serum. When the approximate quantity necessary to produce cornification was found, 3 to 6 additional animals were injected with more closely grouped dosages. Further titrations were conducted if necessary. Six to twelve animals were generally used for each titration, while 3 to 6 animals were injected with dosages very close to the finally accepted value. With the histologic technique and the use of a total of 3 animals for a given dose range, quite reliable results were obtained which were far superior to those offered by the vaginal smear method.[3] With experience the final dosage can be closely approximated from the partial reaction obtained with smaller quantities, while dosages which produce full uterine estrus are usually at least three times too great.

Gonadotropic Hormone.—A modification of the Aschheim-Zondek test was used for the determination of gonadotropic substances. Whole or diluted sera were injected in 6 divided doses over a period of three days into infantile mice, approximately seventeen days old and 8 to 10 gm. in weight. The animals were sacrificed on the fifth morning. The least amount of serum which would cause the production of corpora hemorrhagica or corpora lutea in 2 of 3 animals was considered as containing one mouse unit (Reaction 2 and 3, Zondek[4]). The ovaries were inspected with the aid of a hand lens, but any suspicious specimens were sectioned for histologic examination. It was found expedient to recognize either corpora hemorrhagica or corpora lutea as end points in these titrations, because in some specimens the amount of follicle-stimulating hormone could be detected in higher dilutions of serum than could the luteinizing factor, although it must be recognized that their clinical significance may prove to be quite different. Increase in ovarian weight was not considered as a reliable means of titration, since the gonadotropic substance of pregnancy serum apparently causes only a limited increase.[5]

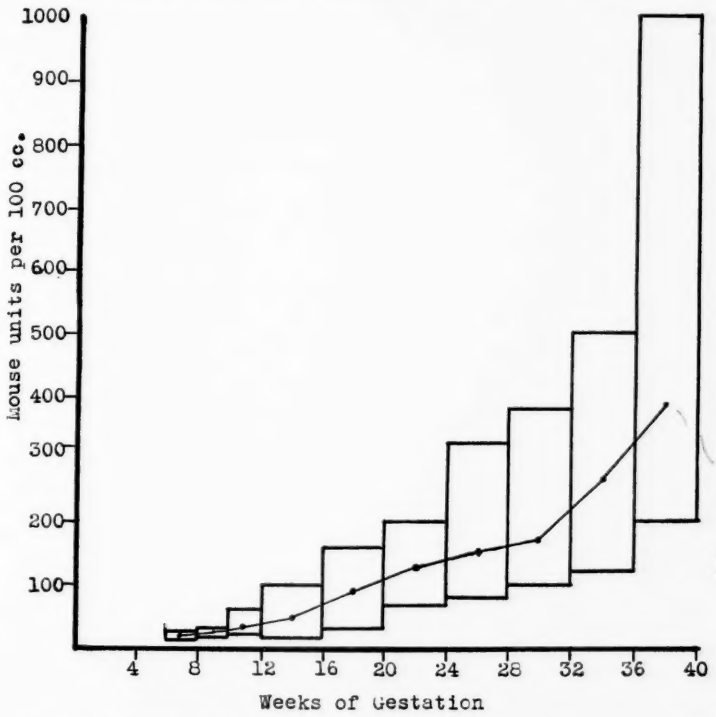

Fig. 1.—Serum estrogen in normal pregnancy. Composite graph of 162 determinations among 40 patients. Rectangles represent range of values, curve represents average values.

In further studies in early pregnancy, we have found concentrations of over 3,000 M.U. in several patients between the sixth and tenth weeks of gestation, indicating that the values for this period are considerably higher than given above. Apparently in some patients a peak is reached some weeks earlier than in others.

RESULTS

1. *Normal Pregnancy.*—Composite graphs were prepared of the values for serum estrogen on 162 determinations among 40 normal pregnant women in various stages of gestation, each patient being tested every two to four weeks for periods of two to six months (Fig. 1).

Preliminary data[1] have been presented of our titrations of the estrogenic content of unextracted blood serum in various stages of pregnancy. These correspond roughly with the results obtained on extracted whole blood by Smith[6] except

that our values were roughly twenty times higher. This is undoubtedly due to loss of the hormone by extraction, since it has been demonstrated by Kemp and Bjergaard[7] that the blood estrin is practically equally divided between the corpuscles and the plasma.

Before the eighth week of pregnancy a full mouse unit usually cannot be demonstrated in less than 4 c.c. of serum, while in some instances the amount of serum containing a full mouse unit was greater than was tolerated by the animal, so that values were estimated by interpolation from partial reactions. Between the eighth and tenth weeks there was an average of 24 M.U. per 100 c.c. Thereafter the concentration continued to rise steadily. From the fourteenth to the twentieth weeks, many patients exhibited a sudden sharp rise which frequently coincided with the sudden fall in gonadotropic substance at this time. Another sharp rise often oc-

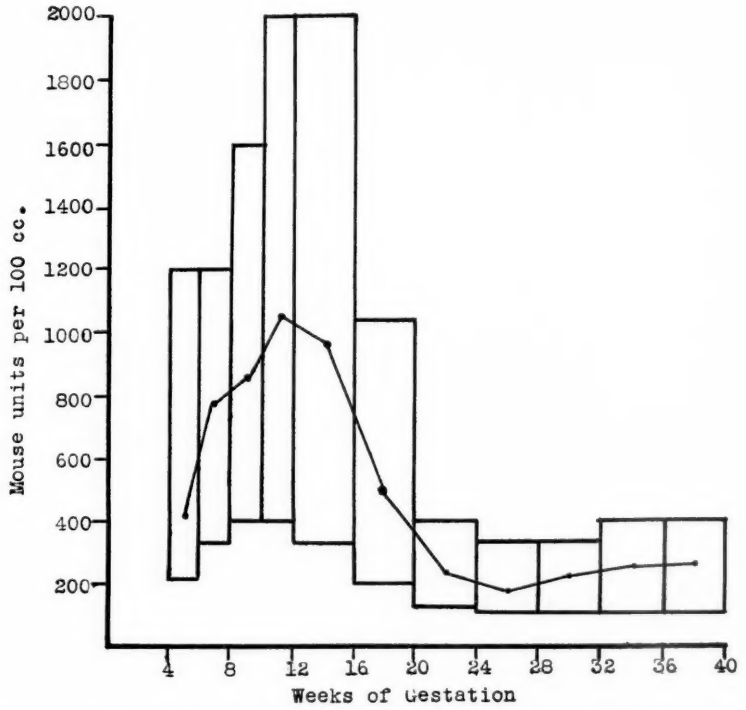

Fig. 2.—Serum prolan in normal pregnancy. Composite graph of 162 determinations among 40 patients. Rectangles represent range of values, curve represents average values.

curs between the thirty-second and thirty-sixth weeks. At term more than 500 M.U. per 100 c.c. of serum is frequently present, perhaps in preparation for the large amounts which seem to be necessary to sensitize the uterus for the onset of labor.

The present consensus is that from almost the very beginning of pregnancy the estrogenic hormones are formed by the placental tissue; the latter structure according to Newton[8] and Collip[9] contains two and perhaps three estrogenic substances in high concentration. Thus even after double oophorectomy in early pregnancy the secretion of estrogens continues.

The nature and source of the gonadotropic hormones, which increase so rapidly in the serum in early pregnancy and are excreted in the urine in quantities sufficient to give a reliable test for pregnancy, within two weeks after the first missed period, has long been the subject for controversy. These have been assumed to be formed by the placenta because of the constant association of trophoblastic tissue with

large quantities of gonadotropic substance. As Newton[8] points out, not only does the latter rapidly disappear from the urine and blood after parturition, but in case of incomplete abortion, it persists until all placental remnants have been delivered.

It remained however, for Nagayama,[10] in a recent report to demonstrate the production of gonadotropic hormone, in vitro, in placental tissue cultures. This has been confirmed by Gey and his associates[11] who also found that tissue from a hydatidiform mole grown in culture produced the hormone. It is interesting that Nagayama[10] found no significant quantities of gonadotropic hormone in tissue cultures of the anterior hypophysis of the pregnant rabbit.

Whether the placental gonadotropic substance, which has been termed anterior pituitary-like, differs in any important essential from that of hypophyseal origin has been seriously questioned. The early report of Reichert,[12] which stated that ovulation did not occur in hypophysectomized rats injected with pregnancy prolan, is not in agreement with subsequent work of Smith and Leonard,[13] Zondek,[14] Hill and Parkes,[15] and others.

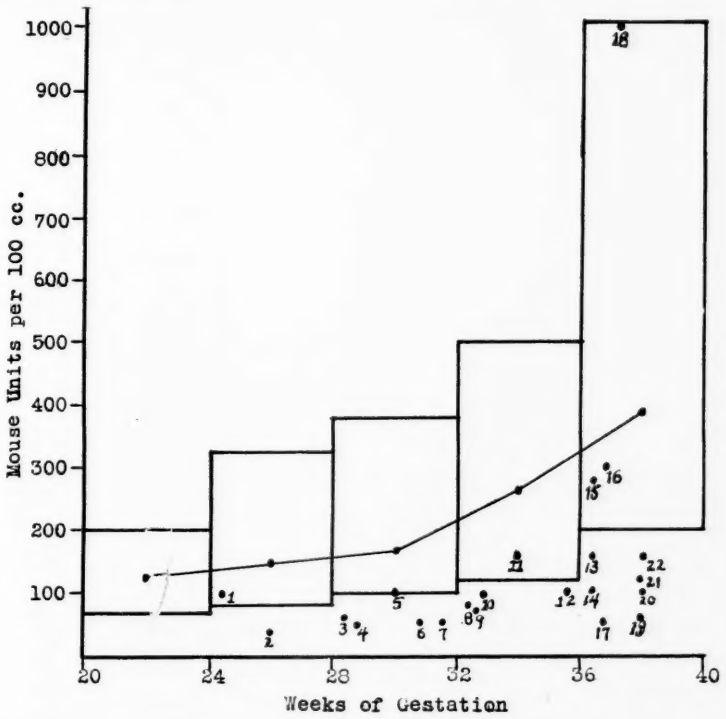

Fig. 3.—Serum estrogen in toxemias of late pregnancy. Rectangles represent range of values in normal pregnancy, curve represents average values in normal pregnancy, numbered dots represent values in toxemias of late pregnancy.

It has been shown that the serum of pregnancy may be used without extraction for the titration of gonadotropic hormone throughout gestation. The character of the curve of the average values is similar to that obtained from extracts of the serum by Boycott and Rowlands,[5] and Smith and Smith.[16] The latter workers state that they employed extracts of the sera and urines for titrations of gonadotropic substances, because they found the injected material to be toxic for immature animals. We have experienced this difficulty in using unextracted urine specimens, but have rarely noted it in the small quantities of sera required for each test during pregnancy. Our values for serum prolan are generally from five to ten times those noted by Smith and Smith on extracted specimens.

It has been pointed out that the rapid rise in concentration of prolan which occurs between the sixth and eighth weeks of pregnancy corresponds to the time when the fetal circulation is established in the chorionic villi, and that it reaches its peak just about the time when the ovary apparently becomes superfluous. Between the tenth and sixteenth weeks of normal pregnancy we have demonstrated the presence of as much as 2,000 M.U. per 100 c.c. of serum. Newton[8] postulates that this may represent a "mass attack" on the ovary to inhibit the follicular system, since the corpus luteum, which probably checks cyclic changes in the first weeks, would probably be incapable of doing so later on.

In the latter half of normal pregnancy the prolan content remains essentially unchanged, although it is in the last trimester in which high values seem to be indicative of dysfunction.

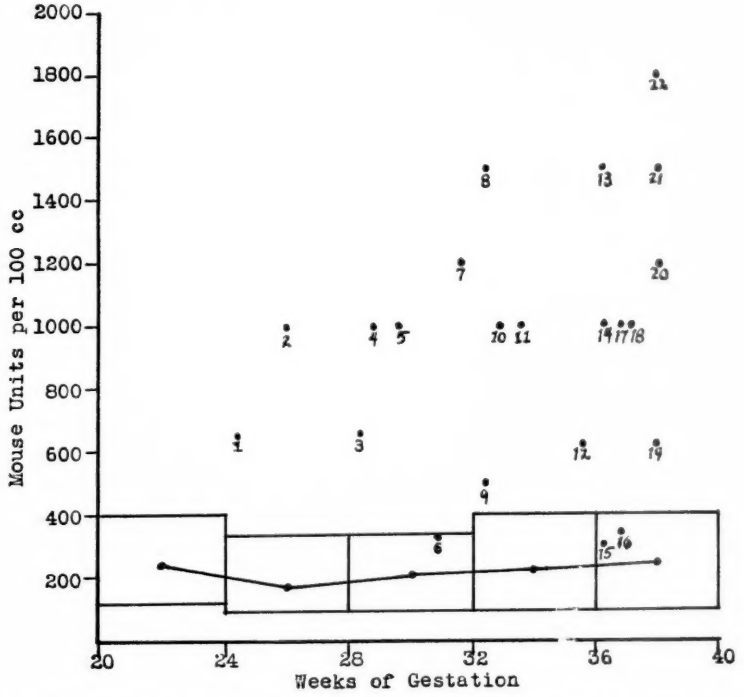

Fig. 4.—Serum prolan in toxemias of late pregnancy. Numbered dots represent same patients as in Fig. 3.

TOXEMIAS OF PREGNANCY

Variations in the sex hormones have not been left unchallenged as an etiologic factor in the toxemias of pregnancy.

Shute[17] has contended that the majority of severe toxemias of late pregnancy, except those of the eclamptic type, are associated with excessive quantities of estrogenic hormone. His statements are based on the detection of excessive quantities of estrogenic substances (in the blood serum) by means of a test utilizing the proteolysis of blood serum.[18] It is stated that when excessive quantities of estrin are present the proteolysis of blood serum by trypsin is inhibited. We have not been able to confirm Shute's work in our laboratory, nor does it seem logical to us that such a test can indicate quantities of estrogen that are "excessive" at any given period when the normal concentration during pregnancy is continually rising.

Smith and Smith[19] have presented excellent quantitative studies on a small group of normal patients and a larger group of toxemic patients which demonstrated that the late toxemias of pregnancy are regularly associated with high values for prolan and somewhat depressed values for estrogen. A number of similar reports on smaller groups of cases have also appeared in the foreign literature.

Our studies in a group of 22 patients with toxemias of late pregnancy (Figs. 3 and 4) also indicate high prolan and low estrogen values. All of this group complained of symptoms of toxemia, had elevated blood pressures, and showed varying degrees of albuminuria. Sixteen were classified clinically as having pre-eclamptic toxemias and 6 as belonging to the group of "low reserve kidney."

Serum titrations made at the time these patients were admitted to the ward for treatment showed abnormally high prolan values in 19 instances and abnormally low estrogen values in 17 instances. Both prolan and estrogen deviated from the normal in 16 patients. In two instances of apparently mild pre-eclamptic toxemia, the prolan and estrogen values were within normal range. In a third instance, the prolan was within the normal range, and the estrogen was depressed, while normal estrogen and elevated prolan values occurred in three instances. In one of the latter the estrogen was unusually high (1,000 M.U. per 100 c.c.).

For the group at large the severity of the toxemia of pregnancy has not shown any distinct relationship to the amount of deviation in prolan and estrogen values, except that in following the individual cases there was in the majority of instances a fall in serum prolan and a rise in the serum estrogen as the patient improved, while a wider deviation marked relapses. This reciprocal rise and fall in prolan and estrogen, which has been commented upon by Smith and Smith,[19] was rather impressive by its consistency.

It was of interest that the patient with the highest rise in serum prolan (Case 22, 1,800 M.U. per 100 c.c.) was admitted primarily because of marked edema of the extremities and face. This observation may prove to be of significance since two other patients in this group with more than the average amount of edema showed high prolan values (Cases 8 and 13).

Premature separation of the placenta occurred in a patient of this group (Case 17) who had a late onset of pre-eclamptic toxemia. Blood taken at the time of cesarean section showed the serum prolan to be elevated to 1,000 M.U. per 100 c.c. while the serum estrogen was unusually low, 66 M.U. per 100 c.c.

Of special interest were three additional patients originally in the group studied for normal values who developed toxemias in the latter months of pregnancy, and in whom a number of titrations were available before the onset of symptoms (Table I).

TABLE I. STUDIES ON THREE PATIENTS WHO DEVELOPED LATE TOXEMIAS

PATIENT	WEEKS	SERUM PROLAN	SERUM ESTROGEN	CLINICAL OBSERVATIONS
A. D.	16	800	50	Normal pregnancy
	20	330	100	
	25	200	100	
	28	330	250	
	31	330	400*	
	34	500*	330	
	37	500*	100†	Pre-eclamptic toxemia
	39	600*	400	In ward, improved
J. G.	25	200	120	Normal pregnancy
	29	250	300	
	33	200	200	
	37	1000*	180†	Pre-eclamptic toxemia
	39	500*	120†	In ward, improved
I. L.	20	160	80	Threatened abortion
	21	330	100	Bleeding and pains stopped
	23	330	120	
	27	500*	80	
	32	660*	80†	Impending toxemia?
	35	800*	120†	Pre-eclamptic toxemia
	37	500	330	In ward, improved

*Represents values above normal range.
†Represents values below normal range.

Here the manner in which the serum prolan and estrogen were correlated with the clinical course was more apparent. In one instance abnormally high values preceded the clinical onset of toxemia by three weeks. In another patient who was being studied for repeated miscarriages, high prolan values also preceded the onset of a moderately severe pre-eclamptic toxemia.

Nephritic Toxemia.—Three patients with nephritic toxemia were available for study, of which two deserve special mention.

CASE 1.—G. T., colored, aged 42 years, gravida ix, registered in the sixth lunar month of pregnancy with a history of severe nephritic toxemia in her last pregnancy. The blood pressure was 192/118, albumin +++, and hyaline and granular casts were present in the urine. Nonprotein nitrogen was 91 mg., creatinine 5.1 mg., and uric acid 5.44 mg. per 100 c.c. Urea clearance was 13 per cent average normal. Liver function tests were normal.

The serum prolan was elevated to 1,200 M.U. and remained the same on a second examination one week later. Serum estrogen was moderately low on the first examination (50 M.U. per 100 c.c.) and had fallen to 33 M.U. on the second examination.

This patient signed her release from the hospital refusing further treatment. Two months later she developed eclampsia post partum and died.

CASE 2.—M. H., colored, aged 18 years, gravida ii, registered in the fourth lunar month of pregnancy with a history of nephritic toxemia and eclampsia in the last pregnancy one year earlier. In the interim she had been under treatment for syphilis and glomerulonephritis. The blood pressure throughout pregnancy ranged from 96/48 to 134/80. There was a consistent mild albuminuria and occasionally red blood cells and casts in the urine. The liver and kidney functional tests were normal. By rigid prenatal care this patient was carried along to term with only one admission to the hospital for impending nephritic toxemia, although there were signs and symptoms of mild toxemia throughout the pregnancy. Serum estrogen and prolan were titrated at frequent intervals, and it is significant that both deviated from the normal range on only two occasions, coinciding with exacerbations in the patient's condition.

Hormone studies were not conducted on the third patient until she was readmitted to the ward at the seventh lunar month with an exacerbation of nephritic toxemia for the fourth time during the gestation. Her serum prolan was very low, 50 M.U. per 100 c.c., which was accounted for by the fact that two days later she was delivered of a macerated fetus.

Indeed we have found that wherever fetal death is suspected, especially in patients with threatened abortion, the quantitative serum prolan determinations repeated at frequent intervals furnished a reliable indication as to the prognosis for the fetus. A continual fall in the serum prolan below the normal range usually indicated death of the fetus, despite the fact that the Friedman test may remain positive for some time. The Friedman test usually becomes negative when the serum prolan has fallen to 50 M.U. or lower.

Smith and Smith[19] have suggested that hormone studies may prove of value in distinguishing true toxemias from "nephritic conditions" complicating pregnancy since in two nephritic patients in their group the serum prolan was normal. Our observations would indicate that although nephritis itself apparently does not influence serum prolan concentration, this becomes raised before or coincident with the onset of toxemic symptoms in these patients.

Pernicious Nausea and Vomiting.—Thus far we have had the opportunity of studying only one such patient. E. K., aged 25 years, gravida i, was admitted to the ward at the fourth lunar month because of marked vomiting, a loss of weight of five pounds during the gestation, slight jaundice and acetonuria. In contrast to the late toxemias of pregnancy, the serum prolan was below the normal range for the period of gestation (80 M.U.) while the serum estrogen was normal (100 M.U. per 100 c.c.). This patient improved rapidly under therapy and the serum prolan two weeks later had risen to 180 M.U. per 100 c.c.

On the other hand the Smiths[19] have suggested that nausea and vomiting is associated with low serum estrogen values, since in five cases of nausea and vomiting

they found low levels of estrin in four and noted a marked rise accompanied by the cessation of these symptoms in all five. It is apparent that further studies on such patients are required.

It may be noted from these studies that the rather constant range of gonadotropic hormone in the latter half of pregnancy renders its routine determination in patients with toxemias of pregnancy more convenient and perhaps more reliable than estrogen values. Furthermore the prolan values can be obtained more quickly and conveniently since histologic preparations are rarely required, nor is it necessary to have castrated animals on hand. With our present technique we regard positive Aschheim-Zondek reactions obtained with quantities of sera less than 0.25 c.c. as being distinctly abnormal in the latter half of pregnancy. Furthermore, since the prolan values were somewhat more closely associated with evidence of toxemia than were the estrogen determinations, it would appear that the endocrine changes can in most instances be followed as readily from serum prolan determinations alone.

The association of an endocrine dyscrasia with the toxemias of pregnancy suggests that the former may be of etiologic significance. However, it is apparent that until we become better informed as to the sources of the sex hormones during pregnancy, and the mechanism which regulates their characteristic rise and fall, the ultimate source of any dysfunction will remain obscure. The influence of estrogenic and gonadotropic hormones on progesterone, and vice versa as well as their effect on many other hormones, also requires investigation.

It is to be noted that the high concentration of prolan per se can hardly be cited as the cause for the manifestations of toxemia, since even higher concentrations normally occur in the early weeks of gestation, while it might be further observed that in early pregnancy the estrogen values are even lower than those associated with toxemia.

CONCLUSIONS

It has been demonstrated that biologic assays for serum estrogen and prolan in pregnancy may be conducted with from 20 to 50 c.c. of blood by a technique which is not only simpler but considerably more accurate than the usual extraction methods. Although there is a considerable deviation of estrogen and prolan values in the various periods of normal gestation, these generally fall within a given range.

In the toxemias of late pregnancy the serum prolan values are usually high for the period of gestation, while the estrogen values are below the normal range. The degree of abnormality in these values does not appear to be related to the severity of the toxemia, nor to any one clinical symptom, except, perhaps, to degree of edema. The onset of toxemia appears to be preceded by a rise in serum prolan, and later by a fall in serum estrogen, while improvement in the clinical condition is followed by a return of these values to the normal range.

Nephritis complicating pregnancy does not appear to be associated with abnormal serum estrogen and prolan values, except when accompanied by toxemia. In nephritic toxemia the serum prolan was elevated and the serum estrogen lowered.

Pernicious nausea and vomiting in one patient was associated with a low prolan and normal estrogen determination, indicating that the endocrine dysfunction differs in the early and late toxemias of pregnancy.

Repeated serum prolan values are of aid in determining the fate of the pregnancy where death of the fetus is suspected.

SUMMARY

I. A technique is described for the biologic titration of estrogenic and gonadotropic hormones in the serum of pregnant women which requires from 20 to 50 c.c. of blood.

a. Estrogenic hormone was assayed by a modification of the Fluhmann technique.

b. Gonadotropic hormone was titrated by a modification of the Aschheim-Zondek test.

c. Whole sera were used as the test solutions and mice as the test animals.

II. The estrogen and prolan values on unextracted sera are much higher than those obtained on extracted specimens.

III. Serum titrations repeated at frequent intervals gave much more consistent results than those obtained from urinary assays.

IV. A total of 162 serum titrations were conducted on 40 normal pregnant women in various periods of gestations, and graphs were prepared showing the normal range and average values from the fourth weeks of gestation to term.

V. Serum titrations conducted on a group of 22 patients with toxemias of late pregnancy usually showed abnormally high prolan and low estrogen values. The severity of the toxemia did not appear to be directly related to the degree of abnormality in prolan and estrogen values, except that those patients with marked edema showed unusually high serum prolan readings. Improvement in the clinical condition was generally associated with a return of the estrogen and prolan values to the normal range.

VI. Studies on three patients in whom titrations were available before the onset of toxemia showed in two instances high prolan values preceding the onset of toxemia by several weeks. These were later followed by low estrogen values.

VII. There was generally a reciprocal relationship between the rise and fall of estrogen and prolan.

VIII. Three patients with nephritic toxemia showed high prolan and usually low estrogen values during the period of clinical toxemia. However one patient with glomerulonephritis, who had a history of nephritic toxemia and eclampsia in the previous pregnancy, showed normal values for estrogen and prolan, except during two periods associated with signs and symptoms of toxemia.

IX. Where intrauterine fetal death was suspected repeated serum prolan studies furnished a better means of determining the fate of the fetus than did the Friedman test.

With our technique when the serum prolan fell to 50 M.U. per 100 c.c. or less the Friedman test usually became negative.

X. One patient with pernicious nausea and vomiting had a low serum prolan determination while the serum estrogen was normal.

The excellent studies of Taylor and Scadron also dealing with the concentration of the sex hormones in the late toxemias of pregnancy have appeared (AM. J. OBST. & GYNEC. 37: 963, 1939) since this paper was submitted for publication.

I am indebted to Dr. Norris W. Vaux for numerous helpful suggestions and facilities which made this study possible.

REFERENCES

(1) *Rakoff, A. E.:* Proc. Soc. Exper. Biol. & Med. **40:** 195, 1939. (2) *Fluhmann, C. F.:* Proc. Soc. Exper. Biol. & Med. **31:** 54, 1933. (3) *Deckert, E. F., Mulhall, E., and Swiney, C.:* J. Lab. & Clin. Med. **23:** 85, 1937. (4) *Zondek, B.:* Hormone des Ovariums und des Hypophysenvorderlappens, ed. 2, Vienna, 1935, Julius Springer. (5) *Boycott, M., and Rowlands, I. W.:* Brit. M. J. **1:** 1097, 1938. (6) *Smith, M. G.:* Bull. Johns Hopkins Hosp. **41:** 62, 1927. (7) *Kemp and Bjergaard:* Endokrinologie **13:** 156, 1933. (8) *Newton, W. H.:* Physiol. Rev. **18:** 419, 1938. (9) *Collip, J. B.:* Internat. Clin., Ser. 42, **4:** 51, 1932. (10) *Nagayama, A.:* Nagasaki Igakkwai Zassi **15:** 12, 1937. (11) *Gey, G. G., Seegar, E., and Hellman, L. M.:* Science **88:** 306, 1938. (12) *Reichert, F. L.:* Am. J. Physiol. **100:** 157, 1932. (13) *Smith, P. E., and Leonard, S. L.:* Proc. Soc. Exper. Biol. & Med. **31:** 744, 1934. (14) *Zondek, B.:* J. Physiol. **81:** 472, 1934. (15) *Hill, M., and Parkes, S. A.:* J. Physiol. **71:** 36, 1931. (16) *Smith, G. V., and Smith, O. W.:* Am. J. Physiol. **107:** 128, 1934. (17) *Shute, E.:* Surg. Gynec. Obst. **65:** 480, 1937. (18) *Idem:* Am. J. Obst. & Gynec. **35:** 970, 1938. (19) *Smith, G. V., and Smith, O. W.:* Surg. Gynec. Obst. **61:** 27 and 175, 1935.

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DISCUSSION

DR. NORRIS VAUX.—This work is going to be of great value to us in the toxemias and in the matter of miscarriages and early abortions. Dr. Rakoff's work has pointed out that there is usually a definite endocrinologic cause for these interruptions of pregnancy, and also that we can prognosticate a possible oncoming toxemia. His work has added a modification to technical methods in that it has shortened the rather tedious histologic technique and avoided the extraction of the twenty-four-hour urine specimen. While the estimation of prolan and the estrogens were run on the serum, urinary assays were undertaken as controls and, as Dr. Rakoff told you, he found the newer method much less expensive, as well as a great saver of time. In using smaller animals, much less blood from the patients is required.

The greatest importance of this work is that endocrinology has been further applied in a clinical manner to obstetrics. A normal range of rise of prolan in the early months with later a gradual fall has been demonstrated. With the formation of the placenta there is a beginning estrogen rise. If in the early months of pregnancy the estimation of prolan is low, there is something wrong, and we can prognosticate an early abortion or miscarriage. If estrogen readings are low in the latter months then these patients will show early toxemia. In a few instances where nephritic toxemia was present, these low readings were also found to be present.

DR. CHARLES MAZER.—I want to call attention to the fact that the test described is not a modification of the Fluhmann test for estrogenic substance. Fluhmann employs mucification of the vaginal mucosa of the rodent as a criteria of estrogenic activity. That permits detection of smaller quantities of estrogen than the Allen-Doisy test, which Dr. Rakoff is employing. It is immaterial whether the final result is ascertained by microscopic examination of the vaginal mucosa or by the vaginal smear method.

The advantage of determining simultaneously, the amount of estrogen excreted in the urine is mainly in the fact that both the quantity of active and combined estrogens can thus be determined, whereas in blood studies the quantity of active estrogens is determinable.

DR. FRANKLIN L. PAYNE.—The establishment of normal values for the chorionic and estrogenic hormone in the blood serum and urine during the various stages of pregnancy will prove to be immensely useful to the clinician. By quantitative serum studies he was able to diagnose intrauterine fetal death. Frank has stated that this fetal death is accompanied by a precipitous drop in the estrin contents of the blood. It would be interesting and of clinical value to learn which of these substances decrease first. Of equal importance is the application of these normal figures in the hormone diagnosis of hydatidiform mole and chorioepithelioma. While neither of these conditioons is always attended by characteristic hormone values in the blood or urine, it is by contrasting such values with the normal concentrations that diagnosis may be facilitated.

DR. RAKOFF (closing).—Strictly speaking, the method of biologic assay for estrogenic hormone employed in this study is not a modification of Fluhmann's method in that vaginal cornification is the end point sought. However, where a number of ascending dosages of serum are used, mucification is the first evidence of estrogenic activity, and was regularly sought for as a point from which higher dosages were calculated. These showed further degrees of hyperplasia to the point of cornification. Even larger dosages were recognized by the production of uterine estrus, so that a number of methods must be combined to reach an end point with the least waste of serum and of animals.

As to the question concerning the presence of free and combined estrogenic substances, this was determined only in those instances in which urinary assays were made, the total estrogenic material being determined by the usual method of acid hydrolysis. In the serum titrations only the estrogenic activity of the whole unextracted serum was determined, since in our experience any type of extraction or hydrolysis lowered the total estrogen content.

As to the concentration of estrogenic hormone in patients with abortion, our experience thus far has been that prolan concentration falls first, and is then followed by a diminution in estrogen. We feel that the prolan values are more valuable in the prognostication of intrauterine fetal death.

Although we have not had the opportunity of studying the serum values in hydatidiform mole, two patients with chorionic tumors of the testicle with metastases were studied. In one the serum prolan was much higher than is obtained in normal pregnancy; in the other the increase was not very much. Indeed in the latter case the Friedman test was negative.

THE GROWTH OF FETUS AND INFANT AS RELATED TO MINERAL INTAKE DURING PREGNANCY

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THE prevalent idea that the maternal organism can, independent of the diet, supply from her tissues a mineral nutriment optimum for the developing fetus needs to be qualified. It appears to be one of the many statements handed down in medical literature which is difficult to disprove because of the lack of sufficient experimental data. Apparently, the human organism has a wide range of adaptability, and the partial insufficiency of one or more minerals supplied to the fetus may not produce any visible clinical signs in the young infant. The optimum development, however, may have been interfered with, and deviations from the normal seen during the early postnatal period may be the direct effect of congenital conditions. It is the purpose of this paper to summarize what is known about fetal mineral content and to show from experimental and clinical sources what positive relationships exist between the growth of the offspring and the mineral intake during pregnancy.

To date, published data on the chemical composition on some 120 fetuses are available. Excellent and comprehensive summaries on mineral retentions of the fetus have been made by Coons and coworkers and by Macy and Hunscher.[2] Supplementary studies have been published recently dealing with the composition of fetal bone[3] and fetal iron.[4] This paper would become too long and unwieldy if all the known mineral elements of body composition were to be discussed. Therefore, it seems

advisable to consider in more detail only the retentions of nitrogen, calcium, phosphorus, and iron.

It may be assumed: (1) that the average nutritional requirements of the fetus with respect to nitrogen, calcium, phosphorus, and iron are shown by the analyses of the fetal composition; and (2) that such analyses show the variations in composition during any period of fetal growth.

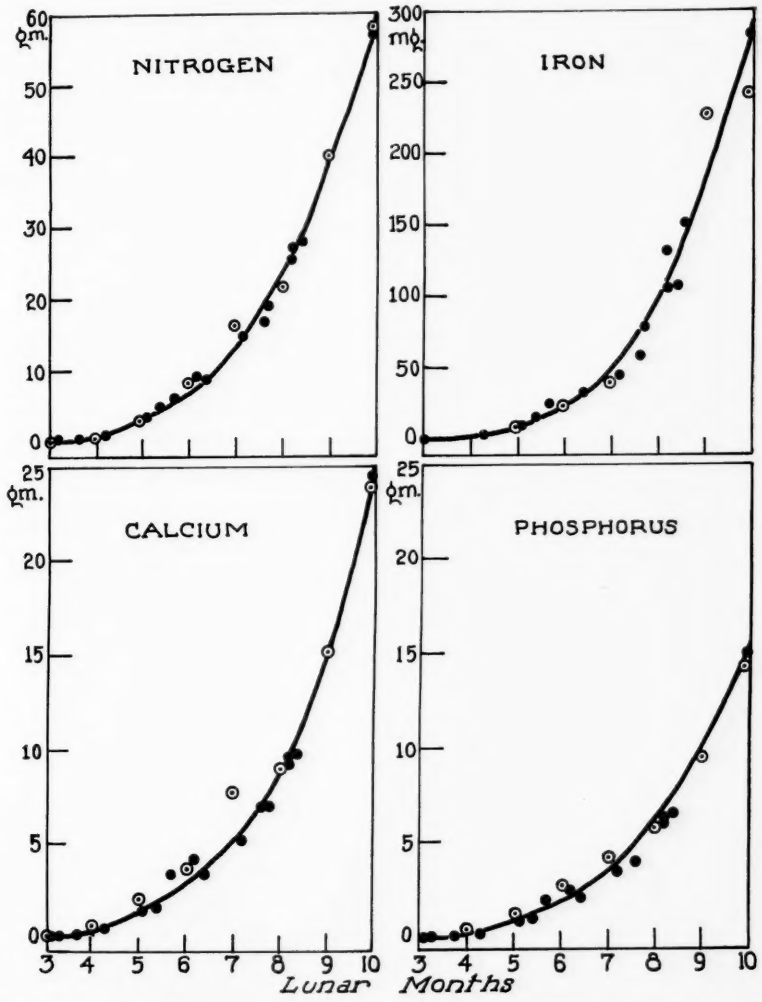

Fig. 1.—Shows the content of nitrogen, calcium, phosphorus, and iron of the fetus from the third to the end of the tenth lunar month. In all of the curves the author's data are represented by the solid dot.

The material analyzed in an investigation of this type deserves some consideration. In most instances some adverse condition is responsible for the interruption of pregnancy or the early death of the premature infant. Apparently, the material analyzed must be chosen with much care since dehydration and starvation change the measurements of

weight and length of the fetus which determine fetal age. It will be shown by the growth graphs for nitrogen, calcium, phosphorus, and iron that if curves were constructed from earlier data[1] slight variations would appear when these figures are compared with results from more recent determinations.[5] The differences may be due principally to three factors, (1) analytical methods, (2) variation in body composition, and (3) the difficulty in obtaining exact body measurements. The last factor becomes very important in any calculation where absolute increase in weight is plotted against time.

In Fig. 1 are shown the curves for nitrogen, calcium, phosphorus, and iron. Some slight discrepancies between the two groups of data for nitrogen are to be noted before the eighth lunar month. It is suggested that the differences found here and in the two following curves, may be due to difficulties suggested in the preceding paragraph. Apparently nitrogen retention for the last two lunar months is 62 per cent of total body content of the term fetus.

For calcium the differences, although greater, are found during the same lunar months as for nitrogen. It will be seen from the curve that the calcium retained in the last two months is 65 per cent of the total body content of the term fetus.

The two groups of data obtained for phosphorus are in close agreement. About 64 per cent of the total phosphorus content of the term fetus is retained during the last two months of pregnancy.

The data for iron obtained from eighteen fetuses analyzed at various ages are compared with values published by Macy and Hunscher.[2] The curves are identical except for the term fetus. It appears from these data that the iron retention during the last two months of pregnancy is 67 per cent of the total fetal iron at term.

It may be said that these retention growth curves all exhibit a similar pattern. Further work will undoubtedly show that they do not represent the optimum mineral retentions, but the agreement found for values so far published would indicate that a working average has been obtained. Also, the smoothness and slope of the curves indicate that mineral increase during the fetal period is a steady continuous process.

In the early months of fetal life, as shown by the mineral curves, the nutritive demands upon the mother are small, and it would be reasonable to assume that fetal needs are readily supplied. Contrary to this assumption are the findings of Schmitz[6] who, after the World War, found consistently lower figures for calcium content of young fetuses from undernourished mothers. Confirmation of these figures would be of practical importance, since it would indicate that a poorly nourished mother who is on a starvation diet may be unable to supply the fetus even in the early months. If the fetus must depend on decalcification of the mother's skeleton or on her low iron stores, it would appear that in this respect gestation takes on a pathologic aspect.

THE MINERAL METABOLISM OF THE RAT

Calcium and Phosphorus.—The following paragraphs barely touch upon the literature of this subject. The review is intended only to emphasize the findings of a few of the more recent studies.

In 1930 we found that newborn rat pups of equal weight differed considerably in their calcium and phosphorus content. This finding suggested a further investigation to determine if changes in the diet of the pregnant rat could noticeably affect the mineralization of the offspring. A preliminary report of this work was published in 1932. It showed that even on an adequate diet the addition of vitamin D caused an increase in the calcium and phosphorus contents of the rat pup. In the same year Nicholas and Kuhn[8] showed that when 0.5 c.c. of viosterol was given daily to pregnant rats on a basic diet the offspring had a slightly higher calcium content than that of young born of control rats; and that when the basic diet was deficient in minerals and vitamin D, the calcium content was less than for the controls. The phosphorus content, however, was approximately the same as that of the controls with either type of diet. In 1935 we published a statistical report[9] on the mineral analyses of several hundred rat pups. In the first three columns, Group A of Fig. 2, are shown graphically the results of that study. The basic diet plus vitamin D as viosterol or as found in cod liver oil increases the body content of both calcium and phosphorus. In 1936 Sontag, Munson and Elton[10] attacked other aspects of this

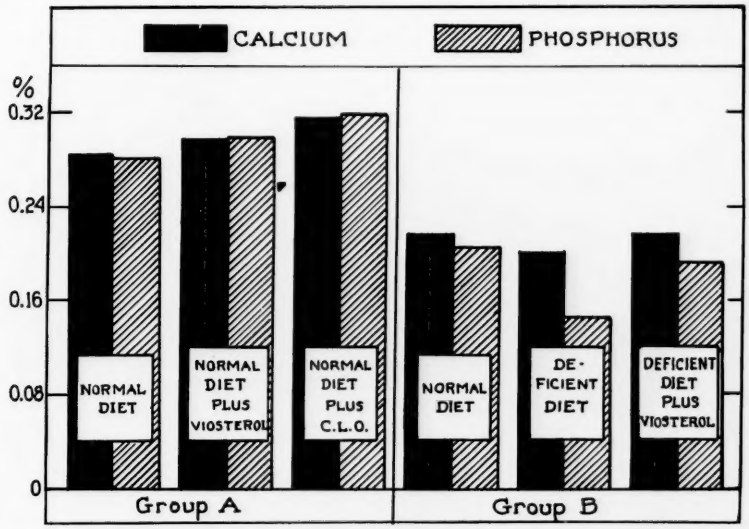

Fig. 2—Illustrates the effect of changes in the diet of the pregnant rat on the calcium and phosphorus content of the offspring.

problem. They showed, as graphically illustrated by the last three columns, Group B, in Fig. 2, that pregnant rats on a diet deficient in calcium and phosphorus gave birth to offspring having a lower calcium and phosphorus content than the control rats on an adequate diet; and that therapeutic doses of vitamin D given to pregnant rats on this deficient mineral diet increased the calcium content to normal value but the phosphorus content, though raised, remained below the normal level.

These studies show that the diet of the pregnant rat when fortified by vitamin D can affect the calcium and phosphorus content of the offspring as follows: (1) If the diet is low in the required minerals the body content approaches the normal level; and (2) if the diet is sufficient the normal level is exceeded. Sontag and coworkers[10] concluded from their study that "abnormalities of vitamin D content of the diet of pregnant rats have much the same effect on the offspring of these rats as such a diet would have if administered directly to young rats. The experiment indicates that fetal mineralization is not independent of the mineral metabolism of the rat mother."

Iron.—Parsons, Hickmans and Finch[11] have shown by study of the blood during the lactation period that iron deficient diets of the pregnant rat produced an anemia in the offspring more marked than the usual physiologic anemia of rat pups and

one which was microcytic in type. They further showed that if the iron deficient diet was continued over the period of two pregnancies, the second litter was reared with difficulty, the pups were of subnormal weight and had an even more pronounced anemia than the first litter. Alt[12] has confirmed this work by chemical determination of the iron content of the liver of rats and the total iron content of the offspring. He showed that a diet low in iron caused a marked depletion of the iron in the liver of the mother rat. He showed further that the first litter from rats on a diet low in iron had only one-half the normal iron content and three-fourths of the normal hemoglobin. The second litter from these same rats on continued low iron diet had only one-fourth the normal iron content and one-half the normal hemoglobin value.

The conclusions apparent from the animal studies cannot be used to prove that the same results occur in man, but only to suggest that the same general biologic processes may exist.

THE MINERAL METABOLISM OF MOTHER, FETUS AND INFANT

Calcium and Phosphorus.—No parallel studies are possible for the human being comparable to the experiments briefly mentioned. There are, however, isolated facts and clinical observations which collectively indicate the interdependence of the mother's diet and fetal growth.

The balance experiments on two groups of pregnant women by Coons and others[1] made in widely separated localities (Chicago and Oklahoma) represent the most comprehensive investigations of this kind. A comparative study of the results obtained on these two groups show some interesting values for the retentions of calcium, phosphorus, and iron. For the group in Oklahoma both calcium and phosphorus retentions were much higher than in Chicago. However, the highest retentions of phosphorus were considered insufficient for proper skeletal and soft tissue growth of the fetus. The better retentions by the southern group were not thought to be due to differences in the diets but rather to the greater amount and intensity of the antirachitic activity of southern sunshine. It is interesting to note also that the Ca:P ratios of the diets were approximately 1:1 whereas the ratios of the amounts retained, of these two minerals, varied from 0.23 to 3.07. This observation illustrates the selective tendency of the organism irrespective of dietary composition. With respect to iron retentions the groups were reversed. Twice as much iron was retained by the northern women. Apparently the iron content of the diets for the two groups was approximately the same. Of interest also are the few comparisons of growth and development of the infants born to the two groups of mothers. Considering only

TABLE I. THE CALCIUM AND PHOSPHORUS OF THE HUMAN FETUS IN GRAMS PER KILOGRAM OF DRY, FAT-FREE SUBSTANCE

FETUS	AGE LUNAR MONTHS	CALCIUM GM.	PHOSPHORUS GM.
14	3.0	17.6	17.0
13	3.2	32.0	22.5
12	3.7	27.1	24.0
17	4.3	29.9	20.1
15	5.1	41.2	29.1
9	5.4	40.7	28.4
6	5.7	57.4	35.9
5	6.2	49.3	30.9
8	6.4	42.7	29.0
11	7.2	40.3	27.7
1	7.6	48.2	28.8
10	7.7	40.3	27.1
2	8.2	38.6	26.0
4	8.2	40.7	28.0
3	8.4	39.4	26.9
7	10.0	46.9	28.8

averages for these two groups, the southern infants weighed a pound more at birth, their teeth erupted earlier and more rapidly, and the infants were advanced in muscular development as shown by lifting of head, sitting, standing and walking.

Much attention has been given to the question of mineral storage of calcium, phosphorus, and iron during the last months of fetal life. While some earlier analyses of the fetus seemed to show that the calcium and the phosphorus content increased faster near term than the solid body substance, recent investigations failed to confirm this conclusion. If a comparison is made of Langstein and Edelstein's[13] figures for calcium and phosphorus content per kilogram of fat-free body substance with those of Camerer and Söldner,[14] the amounts of these minerals for a seven months' and a full-term fetus are about the same. In Table I the absolute amount

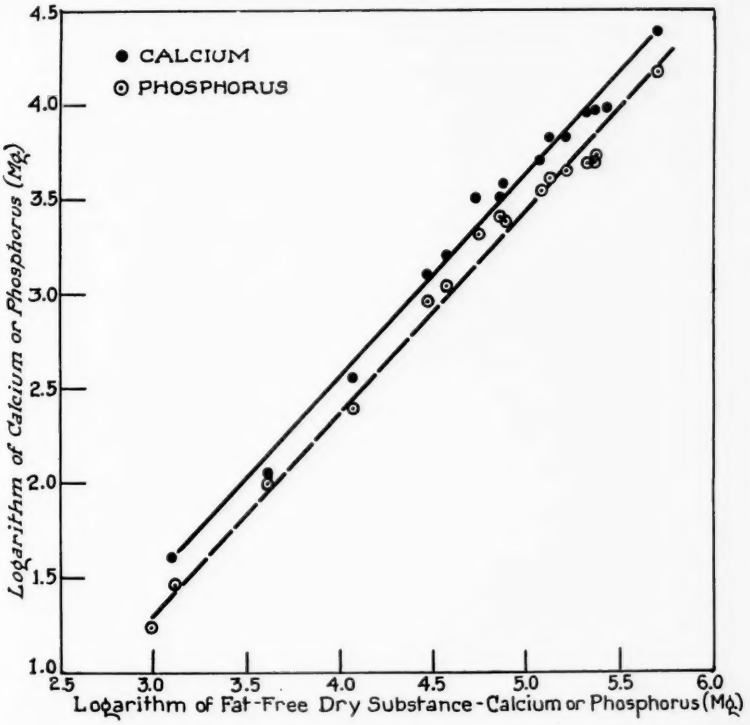

Fig. 3.—Illustrates the relationship between the calcium or the phosphorus content to the fat-free dry body substance (minus the calcium or the phosphorus) of fetuses from the third to the end of the tenth lunar month.

of calcium and phosphorus per kilogram of dry fat-free body substance does not change materially from the fifth to the tenth lunar month. In Fig. 3, the logarithms of the absolute values of calcium and phosphorus plotted against the logarithms of the dry fat-free body substance for each month from the third to the tenth lunar month give parallel and straight lines. This evidence demonstrates that no relative increase of calcium and phosphorus occurs in the last months of gestation. Apparently storage in the strict sense of the word does not take place, but what does occur is an attempt on the part of the fetus to secure optimal mineralization of its skeleton.

During the period of early infancy balance experiments indicate that the calcium and phosphorus retentions are much lower than in the last weeks of fetal life. Since the average birth weight increases 100 per cent in the first five months, the skeleton, approximately the same proportional part of the body, must also grow rapidly. Con-

sequently, the new body substance and particularly the bone formed must be poorer in calcium and phosphorus. Apparently then the growing bones are in a state of continuous change and the minerals of the skeleton in a labile state permit growth of bone until the mineral retentions from the food become adequate. The early development of rickets, more often in the premature than the term infant, depends upon at least three factors: (1) the mineral content of the fetal skeleton; (2) the rapidity of skeletal growth; and (3) the length of time necessary for adequate calcium and phosphorus retentions. According to Hamilton[15] calcium retentions in premature infants are very low from the first to the fifth month. This fact and the greater growth urge predispose the premature infant more certainly to rickets.

At the present time rickets furnishes the best evidence of the interdependence of fetal and infantile skeletal growth and the mother's diet. Coons[1] and others suggest that the low calcium content of fetuses reported by Schmitz[6] soon after the World War was due chiefly to the undernourished condition of mothers. In 1926 Greenebaum and coworkers[16] reported the incidence of rickets in two groups, each containing 25 infants. A comparative study showed that the occurrence and degree of rickets were markedly less in the group where the maternal diets were made adequate. They concluded that "if the diet of the mother during the last three months of pregnancy can be made approximately correct in caloric and mineral intake, while it will not prevent rickets, it will have a controlling influence on the development of the disease in her offspring."[11]

TABLE II. FETAL IRON

FETUS WEIGHT GM.	BODY CONTENT		FETUS WEIGHT GM.	LIVER CONTENT	
	FAT-FREE DRY SUBSTANCE MG. PER KG.	TOTAL PER FETUS MG.		DRY SUBSTANCE MG. PER KG.	TOTAL PER LIVER MG.
14	712	0.7	162	1333	1.7
115	469	6.0	530	1183	6.7
259	300	10.6	750	1980	18.4
335	398	17.2	770	1242	11.0
490	378	24.0	819	1667	11.2
570	384	32.0	860	2470	18.7
1010	433	48.8	860	1130	7.9
960	359	59.2	900	3454	32.2
1205	413	80.6	1295	2470	29.6
1555	355	105.6	1540	3055	44.8
1545	491	134.4	1750	1070	15.4
1615	416	111.0	2670	3160	72.3
2250	400	152.3	2950	3474	117.9
2915	454	284.2	4030	2339	118.5

The most conclusive evidence of inadequate fetal nutrition is the reported cases of congenital rickets and those early cases where insufficient time since birth had elapsed for rickets to develop. Maxwell and others[17] have reported 2 cases in newborn Chinese infants, Dunham[18] has reported 1 case (patient thirty-four days old), and Eliot and Park[19] have reported 8 cases of early rickets in infants two weeks to one month old, diagnosed at autopsy. Rachitic changes have also been noted by Ylppö[20] in newborn premature infants to the extent of 5 per cent. Hess[21] has also occasionally noted on x-ray plates "epiphyses of newborn infants which instead of being sharp are slightly frayed with a tendency to cupping, such as might be termed incipient rickets in later months."

Iron.—The literature on the interdependence of the maternal and the fetal and the infant iron metabolism is more controversial than that of the two minerals discussed. Only very short references will be made to the more important observations bearing on the subject.

In Table II, data are reported on 28 fetuses,[4] 14 for the total body iron and 14 for the content of liver iron. The iron content per kilogram of fat-free dry substance remains practically unchanged during the fetal growth period, but the liver

iron similarly calculated increases in the term fetus. The analyses here summarized, however, do not differentiate between hemoglobin and nonhemoglobin iron of the liver. The figures demonstrate only that even though the liver becomes somewhat less vascular, the iron increases. These results were obtained of fetuses born to women having normal hemoglobin values. The only quantitative studies pertaining to the iron content of the livers of newborn infants born to anemic mothers were made by Toverud.[22] She found a slight decrease in the nonhemoglobin iron content in 8 of 12 infants dying shortly after birth. The values found in the literature for nonhemoglobin iron content of the liver appear to be about 50 per cent of the total liver iron, from 50[23] to 60[22] mg. The importance of this iron store in the liver will become apparent when a comparison is made with other sources of iron.

In recent studies on the blood of newborn infants, the suggestion has been made that the iron obtained from the so-called excess hemoglobin at birth is two to three times the estimated nonhemoglobin iron in the liver. This suggestion, if correct, would minimize the significance of the iron store in the liver. However, calculations based on recent figures for total iron of the body, and hemoglobin values obtained at birth on the cord blood, show that the store of iron in the liver appears to be as large as that from any other source.

In 1937 Fullerton[24] by approximate estimations for iron in the various body tissues at birth calculated the iron content of the newborn infant to be 450 mg. This value is much too high since actual iron determinations on the term fetus give an average figure of 280 mg.[3, 25] Further, the normal newborn infant has a cord-blood hemoglobin value of 16.8 gm.[26] per 100 c.c. This figure drops to 11 gm.[27] per 100 c.c. at the end of two months. Even with the greater blood volume* at the end of the second month the amount of hemoglobin in the circulating blood is 18 gm. less. The decrease of this blood constituent represents the excess hemoglobin from which 60 mg.† of iron may be liberated and stored in the body. If either the mean of the values for the hemoglobin content of the cord blood as found by Guest, Brown and Wing[29] or the mean found one to five hours after birth by Kato and Emery,[27] about 18 gm. per 100 c.c., is taken as an average, the iron from the excess hemoglobin amounts to 80 mg. The difference between this figure and the 60 mg. of nonhemoglobin iron in the liver as 20 mg. This amount is of no significance since the assumed blood volume at birth, 14.7 per cent, may be too high,[25] and the amount of hemoglobin based on 18 gm. per 100 c.c. would contain 280 mg. of iron, the total body content. This is improbable since the nonhemoglobin iron in the full-term fetus is by conservative estimation 60 to 80 mg. Therefore, for all practical considerations, equal amounts of iron may be expected from the excess hemoglobin and from the liver stores.

The importance of the iron stores for the formation of new hemoglobin may be considered. In a normal two months' old infant with 11 gm. of hemoglobin per 100 c.c., approximately 60 gm. of hemoglobin containing 200 mg. of iron, would be in the circulating blood. If, according to Stearns and McKinley,[30] the iron loss of the infant on a cow's milk diet averages from 50 to 75 mg. during the first two months of life, then the hemoglobin iron and iron loss would approximately account for all the iron present at birth. This would either leave the iron body stores completely exhausted or more likely result in the early appearance of anemia. On breast milk feeding, however, the infant is more often in a state of positive, though slight, iron balance as contrasted with the usual negative balance found on cow's milk feeding. It is, therefore, in this latter condition that high iron stores of the liver protect the infant from the hypochromic type of anemia. While the liver store of iron and hemoglobin concentration at birth and the kind of feeding are of importance in the consideration of anemia in early infancy some other factors as: (1) the rapidity of growth, (2) the number and severity of infections, and (3) the use of iron salts in the diet must also be taken into account.

*Blood volume at birth is about 470 c.c., 14.7 per cent of body weight. At two months the blood volume is 550 c.c., 10.9 per cent of body weight (Lucas and Dearing.[28]

†3.35 mg. of iron per gm. of hemoglobin was used to calculate hemoglobin iron (Butterfield[31]).

Several recent publications have stressed the relationship existing between the iron deficiency during pregnancy and the hypochromic anemia that appears before the sixth month of life. This anemia of infancy when not affected by some associated disease is not due to congenital abnormal blood formation since these infants have normal blood at birth.[32] Furthermore, postnatal nutrition of all infants during the first four months is much the same because the food is restricted to milk and vitamin supplements.

In 1931 Mackay[33] published a comprehensive study on nutritional anemia in infancy, in which a comparative study was made between infants born to moderately anemic mothers (54 to 70 per cent hemoglobin) and infants born to mothers with normal hemoglobin values. The infants born to the anemic mothers showed a lower hemoglobin level at every month for the first six months of life than did the infants born to the nonanemic mothers. From this study Mackay concludes that anemia of the mother predisposes the infant to anemia during the first year. A later paper by Neale and Hawksley[34] emphasizes the finding of anemia in twins born to anemic and nonanemic mothers. The demand upon the mother for iron in a twin pregnancy is considerably more than in single pregnancies and even though the mother's hemoglobin may be normal, all her stores may be consumed and one or both of the twins will develop anemia. Finally, the most conclusive study on this subject is that of Strauss[32] since it compares a series of 14 mothers with less than 45 per cent hemoglobin with a series of 12 mothers with hemoglobin over 70 per cent. Statistically there was no significant difference between the two groups of the hemoglobin values at birth. However, when these infants were examined one year later, it was found that the infants born to anemic mothers had an average hemoglobin value of 46 per cent as compared to 67 per cent for the infants born to nonanemic mothers. Strauss suggests the data "indicates that infants born to mothers suffering from iron deficiency although exhibiting at birth a normal blood picture, are unable to maintain a normal hemoglobin level during the first year of life." These investigations demonstrate that maternal iron storage during the period of pregnancy is at fault, since this hypochromic anemia of the infant may be prevented either by iron administered to the mother during pregnancy or by early administration of iron to the infant.

COMMENT

The object of this résumé on the interdependence of the fetal growth and the maternal diet is to emphasize the need for better mineral retention of the offspring. The prevention of rickets should not be used as the only criterion of the vitamin D requirement. According to Jeans and Stearns,[35] "It is at least reasonable to think that the optimum amount of any nutritional essential is somewhat greater than the amount which barely prevents clinical pathological changes." If then, the optimum mineralization of the fetus were more widely known and attempts made to reach this level, freedom from rickets, good growth and development could be assured in early infancy.

The same general relationship holds for iron stores and anemia. If the hemoglobin and iron storage in the liver are high at birth, all other things being equal, the infant stands a better chance of not developing hypochromic anemia during the first year.

It is admitted that treatment of both rickets and anemia may be started in early infancy. However, prophylaxis is more rational and adds a factor of safety. Toverud[22] suggests that "we pediatricians have to feel that our prophylactic work will be more consequent and give better results if we might be able to feed the infant not only from the moment of birth but from the moment of conception."

SUMMARY AND CONCLUSIONS

1. Graphs are shown illustrating body content of nitrogen, calcium, phosphorus, and iron during the last seven lunar months.

2. Metabolism experiments on animals show that the diet of the mother enhanced by vitamin D will increase the transmission of calcium and phosphorus to rat pups. When diets insufficient in iron are given to mother rats a reduction of the iron content of rat pups by one-half will result, and, if diet is prolonged in the same female, the second litter will have only one-fourth the amount of body iron.

3. Metabolism experiments on comparative groups of pregnant women suggest that the vitamin D factor produced by sunlight plays an important part in their mineral retention. The occurrence of congenital and early rickets indicates that mothers may not provide the fetus with sufficient calcium and phosphorus for proper growth of the skeleton. Studies on iron indicate (1) that the normal full-term infant is born with a store of iron in the liver, (2) that this iron source is quite as important as the amount of iron which may be liberated from excess hemoglobin, and (3) that infants born to anemic mothers are subject to hypochromic anemia during the first year of life.

4. Experimental and clinical data, while incomplete in many respects, combine to demonstrate the importance of an adequate diet during the period of pregnancy to promote optimum growth of the fetus and young infant.

REFERENCES

(1) *Coons, C. M., Schiefelbusch, A. T., Marshall, G. B., and Coons, R. R.:* Oklahoma Agricultural and Mechanical College, Agricultural Experiment Station, Bulletin No. 223, March, 1935. (2) *Macy, I. G., and Huncher, H. A.:* Am. J. Obst. & Gynec. **27:** 878, 1934. (3) *Swanson, W. W., and Iob, L. V.:* Am. J. Dis. Child. **54:** 1025, 1937. (4) *Iob, V., and Swanson, W. W.:* J. Biol. Chem. **124:** 263, 1938. (5) *Iob, V., and Swanson, W. W.:* Am. J. Dis. Child. **47:** 302, 1934. (6) *Schmitz, E.:* Arch. f. Gynäk. **121:** 1, 1923. (7) *Swanson, W. W., and Iob, L. V.:* Am. J. Dis. Child. **44:** 477, 1932. (8) *Nicholas, H. O., and Kuhn, E. M.:* J. Clin. Investigation **11:** 1313, 1932. (9) *Swanson, W. W., and Iob, L. V.:* Am. J. Dis. Child. **49:** 43, 1935. (10) *Sontag, L. W., Munson, P., and Elton, H.:* Am. J. Dis. Child. **51:** 303, 1936. (11) *Parsons, L. G., Hickmans, E. M., and Finch, E.:* Arch. Dis. Child. **12:** 369, 1937. (12) *Alt, H. L.:* Am. J. Dis. Child. **56:** 975, 1938. (13) *Langstein, L., and Edelstein, F.:* Ztschr. f. Kinderh. **15:** 49, 1917. (14) *Camerer, W., and Söldner:* Ztschr. f. Biol. **39:** 173, 1900. (15) *Hamilton, B.:* Am. J. Dis. Child. **20:** 316, 1920. (16) *Greenebaum, J. V., Selkirk, T. K., Otis, F. A., and Mitchell, A. G.:* J. A. M. A. **87:** 1973, 1926. (17) *Maxwell, J. P., Hu, C. H., and Turnbull, H. M.:* J. Path. & Bact. **35:** 419, 1932. (18) *Dunham, E. C.:* Am. J. Dis. Child. **26:** 155, 1923. (19) *Eliot, M. M., and Park, E. A.:* Practice of Pediatrics—Brennemann, Chicago, 1936, W. F. Prior & Co., Chap. 36. (20) *Ylppö, A. H.:* Ztschr. f. Kinderh. **24:** 1, 1919. (21) *Hess, A. F.:* Rickets, Osteomalacia and Tetany, Philadelphia, 1929, Lea and Febiger, p. 94. (22) *Toverud, K. U.:* Acta Paediat. (Supp. 1) **17:** 136, 1935. (23) *Sheldon, J. H.:* Brit. M. J. **2:** 869, 1932. (24) *Fullerton, H. W.:* Arch. Dis. Child. **12:** 91, 1937. (25) *Hugounenq, M. L.:* J. Physiol. et de path. gen. **1:** 703, 1899. (26) *Adair, F. L., Dieckmann, W. J., and Grant, K.:* Am. J. Obst. & Gynec. **32:** 56, 1936. (27) *Kato, K., and Emery, O. J.:* Folia haemat. **49:** 106, 1933. (28) *Lucas, W. P., and Dearing, B. F.:* Am. J. Dis. Child. **21:** 96, 1921. (29) *Guest, G. M., Brown, E. W., and Wing, M.:* Ibid. **56:** 529, 1938. (30) *Stearns, G., and McKinley, J. B.:* J. Nutrition **13:** 127, 1937. (31) *Butterfield, E. E.:* Ztschr. f. physiol. Chem. **62:** 173, 1909. (32) *Strauss, M. B.:* J. Clin. Investigation **12:** 375, 1933. (33) *Mackay, H. M. M.:* Med. Res. Counc. Spec. Rep. Series, London, 157, 1931. (34) *Neale, A. V., and Hawksley, J. C.:* Arch. Dis. Child. **8:** 227, 1933. (35) *Jeans, P. C., and Stearns, G.:* J. A. M. A. **111:** 703, 1938.

THE EVALUATION OF THE HUMAN VAGINAL SMEAR IN RELATIONSHIP TO THE HISTOLOGY OF THE VAGINAL MUCOSA

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IN RECENT years, our understanding of the endocrine factors involved in a number of gynecologic conditions has been dependent, in a great measure, upon the development of methods of estimating the functional activity of the ovaries. The introduction of the vaginal smear technique by Stockard and Papanicolaou[1] in 1917 and its application by Allen and Doisy[2] as a quantitative method of assaying follicular hormone, have opened up new opportunities for workers in the field of endocrinology. In the human being, the introduction of quantitative assay methods by Frank and others for the determination of estrogens in the blood and urine has yielded a great deal of information about some of the obscure problems in gynecologic endocrinology. These determinations, however, are time-consuming and costly and necessitate the collection of urine over a period of many days. Furthermore, it is not entirely clear at present how to interpret the estrogen excretion in relation to ovarian function. In our investigations of a group of cases in the out-patient department, we felt the need for a simple method of estimating ovarian function. Papanicolaou's[3] introduction of the vaginal smear technique in human beings seemed to offer a promising solution to the problem.

Papanicolaou[3] has described cyclical changes in the cytology of the human vaginal secretions corresponding to the follicle changes in the ovary. The changes described, however, are slight in degree and require a great deal of experience to interpret. Subsequently, Papanicolaou and Shorr[4] reported that after the menopause and after castration the human vaginal smear reveals striking cytologic characteristics which distinguish it from the smear obtained from women with normally functioning ovaries. They also demonstrated that the smears could be changed to resemble those of the normal cyclical women by the administration of an adequate amount of estrogenic hormone. This method of study of the vaginal secretions offered a simple, direct means of evaluating the estrogenic activity of the human ovaries and the efficacy of administered estrogenic substances. The Papanicolaou technique of preparing the smears we found to be too complicated and time-consuming to be practicable for a busy clinic. Salmon and Frank[5] have described a simplified method of preparing the vaginal smears which enables a reading to be obtained within a few minutes after the smear is taken. Because of the departure from the Papanicolaou technique, we felt it desirable to determine how reliably one can interpret the smears prepared by this method and how accurately they reflect the changes in the vaginal mucosa.

EXPERIMENTAL PROCEDURE

A group of 60 women, who came to the clinic because of menopause symptoms, were selected. Preliminary vaginal smears were taken 3 times weekly for two weeks. At the end of this time, a vaginal biopsy was taken from the left fornix of the vagina. The patient was then given estrogenic hormone therapy either intramuscularly or by mouth. For the intramuscular injections, estradiol benzoate (progynon-B)* in sesame oil was used. The oral preparation was dihydroxyestrin tablets (progynon-DH).* After the preliminary biopsy, estrogen therapy was begun immediately. Smears were then taken 3 times weekly and a biopsy taken from the left fornix of the vagina at the completion of the course of therapy.

TECHNIQUE OF VAGINAL SMEAR STAIN

A speculum is inserted into the vagina and the vaginal mucous membrane and cervix inspected to exclude the presence of any infection. A small amount of the vaginal secretion is aspirated from the surface of the posterior blade of the speculum with a small glass pipette. The secretion is diluted with a little normal saline, spread on a glass slide, allowed to dry in the air and stained for one minute with fuchsin;† the smear is then washed with tap water and is ready for examination.

The biopsies were taken with an ordinary cervix biopsy punch. Of the 60 cases studied, 10 were x-ray castrates, 20 were spontaneous, and 30 were surgical castrates.

VAGINAL SMEAR CLASSIFICATION

The smears were classified into 4 groups to indicate various degrees of estrogen deficiency.

Reaction I.—(Advanced estrogen deficiency.) The characteristic features of this type of smear are the complete absence of squamous epithelial cells and the presence of small, round or oval epithelial cells with rather large, darkly-staining nuclei (''atrophy cells''). These are the cells which Papanicolaou and Shorr have described as ''deep cells.'' Leucocytes and erythrocytes are present in varying numbers (Fig. 1).

In some smears the epithelial cells are few in number and associated with large numbers of leucocytes; in others, particularly in very old women, the epithelial cells are very small, few in number and are associated with a scattering of leucocytes and erythrocytes.

Reaction II.—(Moderate degree of estrogen deficiency.) There is a variable number of large, epithelial cells many of which are irregular in shape. The nuclei are relatively large. Interspersed among these cells is a varying number of ''atrophy cells'' and leucocytes. The relative proportion of the large epithelial cells to the ''atrophy cells'' is variable. What distinguishes this smear from the I and the III is the association of the ''atrophy cells'' with the larger epithelial cells (Fig. 2).

Reaction III.—(Slight degree of estrogen deficiency.) Predominance of rather large irregular epithelial cells is the striking feature of this smear. The cells vary in size and shape, their edges are somewhat irregular and frequently indistinct in outline. They frequently occur in clumps; a few ''atrophy cells'' may be present (Fig. 3).

Reaction IV.—The smear consists of large, flat, clearly-outlined, squamous epithelial cells with small, deeply-staining nuclei. These cells are larger, more clear-cut and the nuclei relatively smaller than those in the III smear. No ''atrophy cells'' and usually no leucocytes are seen (Fig. 4).

The Morphology of the Vaginal Mucosa after Cessation of Ovarian Activity.—Of the vaginal biopsies taken from the 60 cases before treatment, all but one showed

*For the progynon-B and progynon-DH used in this investigation, we are indebted to Drs. Stragnell, Schwenk, and Gilbert of the Schering Corporation, Bloomfield, N. J.

†Reagent:

1.	Fuchsin	3.0
	Alcohol	95 to 100.0%
2.	Alcoholic fuchsin (1)	12.0
	Distilled water	100.0

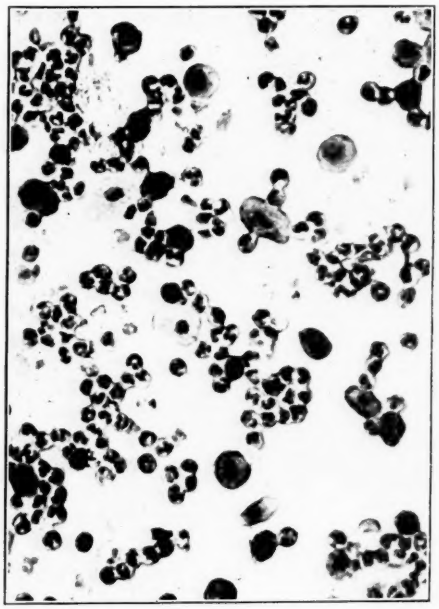


Fig. 1.

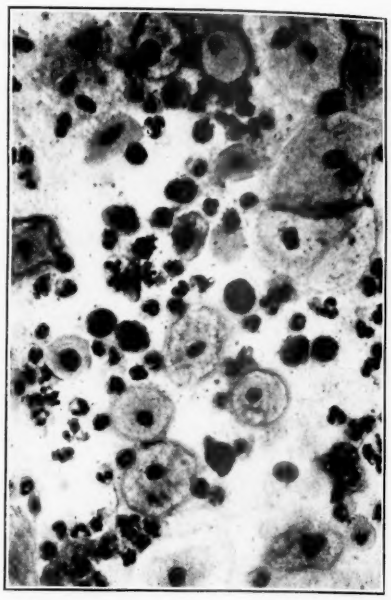


Fig. 2.

Fig. 1.—Reaction I. Advanced estrogen deficiency. Vaginal smear taken from patient B.L., aged 54, nine years after the menopause. The smear contains the typical "atrophy cells," leucocytes, and a few erythrocytes.

Fig. 2.—Reaction II. Moderate estrogen deficiency. Smear taken from patient S.B., aged 48, four years after bilateral ovariectomy. Note presence of moderate-sized epithelial cells as well as "atrophy cells," leucocytes, and erythrocytes.

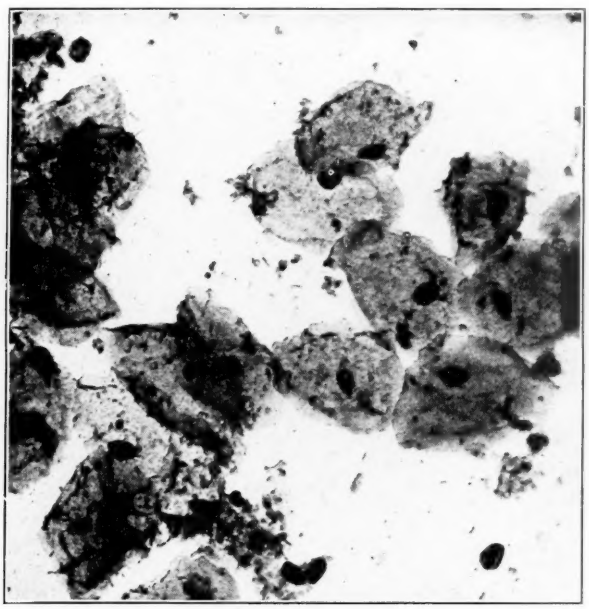


Fig. 3.—Reaction III. Smear taken from patient J.W., aged 43, ten months after spontaneous menopause. The epithelial cells are larger than in the Reaction II smear (Fig. 2). They vary in shape, are irregular in outline and have a tendency to form in clumps.

some degree of atrophy of the mucous membrane. To facilitate classification, the different stages of atrophy were classified into 4 grades.

Grade I: (Most advanced degree of atrophy.) The mucosa consists of a thin layer of epithelial cells which vary in depth from 1 to 6 cell rows. In some areas the epithelium is completely absent. The normal differentiation into layers is lost. There are no papillae and no cornification layer. There are numerous areas of subepithelial round cell infiltration (Fig. 5).

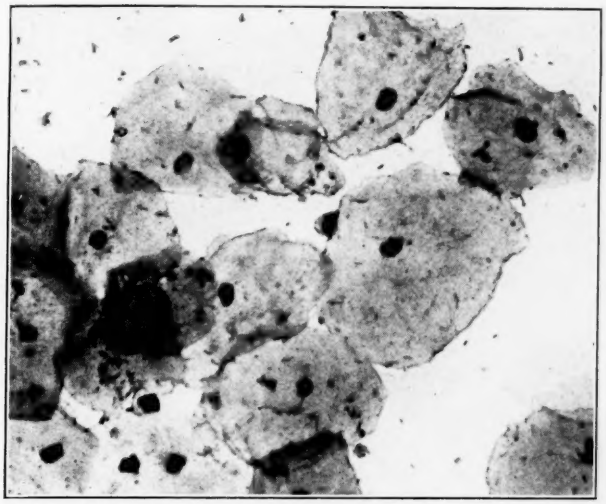


Fig. 4.—Reaction IV. The cells are large and flat; the edges clean cut; nuclei pyknotic. No "atrophy cells" are present. Smear taken on the eighteenth day of the cycle from young woman, aged 23, with a normal, regular menstrual cycle.

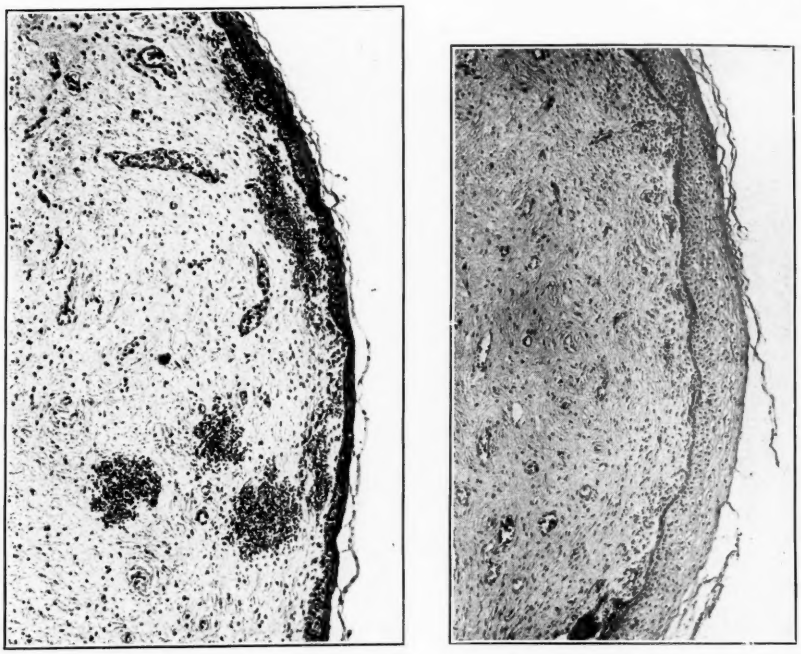
Fig. 5.—Grade I. Most advanced degree of atrophy. Case B.L., aged 54, nine years after the menopause. Note thinness of epithelial layer, absence of differentiation into zones, absence of papillae and cornification. Compare with smear shown in Fig. 1.

Grade II: (Moderate degree of atrophy.) The mucous membrane consists of a much thicker epithelial layer, varying in thickness from 4 to 10 cell rows. Differentiation into basalis and functionalis is present only in some areas and is not sharply defined. The papillae are few in number and are shallow. Cornification is absent (Fig. 6, *A* and *B*).

Grade III: (Slight degree of atrophy.) The mucous membrane consists of 10 to 20 layers of cells; there is definite differentiation into basalis and functionalis. The papillae are, however, shallow and in some areas absent. The cornification zone is usually absent. In some there are small areas of a thin cornified layer (Fig. 7).

Grade IV: This is the typical mature mucous membrane found in normally menstruating women, characterized by division into 3 well demarcated layers. The cornification zone is well defined and the papillae deep and uniformly distributed (Fig. 8).

While the classification of the vaginal mucosa into 4 groups, indicating various degrees of regression of the epithelial layers, was made for purposes of simplification, it should be borne in mind that this grouping is more or less artificial and that not infrequently one can find different degrees of atrophy in the same biopsy



A. *B.*

Fig. 6.—*A* and *B*.—Grade II. Moderate degree of atrophy. Case S.B., aged 48, four years after bilateral ovariectomy. Compare with Smear II (Fig. 2). Note different degrees of atrophy present in two fields of the same biopsy specimen.

specimen (compare Fig. 6, *A* and *B*). *The regressive process apparently does not occur uniformly.* Furthermore, the repair or proliferative process which occurs in response to estrogen administration likewise does not occur uniformly, some parts of the mucosa showing more advanced degrees of proliferation than others.

Correlation of the Vaginal Smear With the Histology of the Vaginal Mucosa.—Before treatment was instituted, an attempt was made to correlate the cytologic features of the vaginal smears with the histology of the vaginal mucosa. The cases in which the vaginal mucosa was Graded I (advanced atrophy) had Reaction I vaginal smears; Grade II mucous membrane (moderate atrophy) had Reaction II smears. On comparing the morphologic characteristics of the mucous membrane of these cases with the corresponding vaginal smears, it becomes apparent that the smears reflect with surprising accuracy and uniformity the status of the vaginal mucous membrane. Thus Reaction I smears (Fig. 1), consisting of the round and oval epithelial cells ("atrophy cells") and numerous leucocytes, are associated with a mucous

membrane exhibiting advanced degree of atrophy (Fig. 5). Similarly, the Reaction II smear, distinguished from the Reaction I by the presence of a significant number of larger epithelial cells in addition to the "atrophy cells" and leucocytes (Fig. 2), is found associated with a mucous membrane showing a less-advanced degree of atrophy (Fig. 6, *A* and *B*). The Reaction III smear (Fig. 3), consisting predominantly of rather large, irregular epithelial cells, has been found in correlation with a mucous membrane revealing the slightest degrees of regression (Fig. 7).

In a number of cases vaginal smears were found which were classified as intermediate between Reactions II and III, consisting of both squamous epithelial cells and "atrophy cells" in varying ratios. Such intermediate smears are probably attributable to the various degrees of atrophy which may occur in different areas of the same mucous membrane.

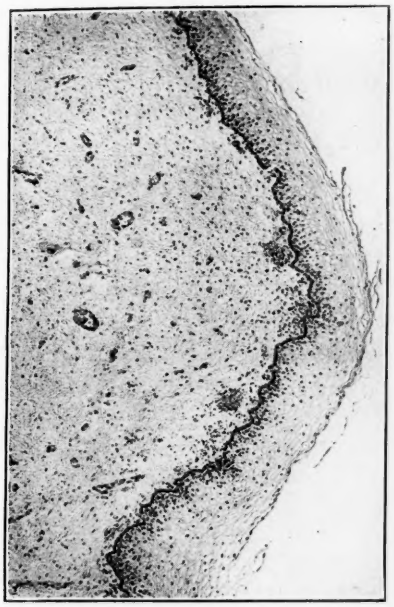


Fig. 7.

Fig. 8.

Fig. 7.—Grade III. Slight degree of atrophy. Case J.W., aged 43, ten months after spontaneous menopause. Compare with Smear III (Fig. 3).

Fig. 8.—Normal mucosa from patient, aged 23, showing typical layering and cornification. Compare with vaginal smear (Fig. 4).

The Effect of Estrogen Therapy Upon the Vaginal Smears and Vaginal Mucous Membrane.—In Fig. 9 is shown the vaginal mucous membrane of Case 4, two weeks after the preliminary biopsy. During these two weeks the patient had taken 120,000 rat units of dihydroxyestrin by mouth. Examination of the vaginal mucosa reveals a striking increase in the entire thickness of the epithelial lining. In the field shown, the epithelial layer varies from 15 to 20 cells in thickness. The basalis is clearly defined and is apparently the site of intense activity. It is noteworthy, however, that in spite of this no cornification can be discerned. In other fields of the same specimen, the mucosa is not as thick but the basilar layer shows the same proliferative activity. The corresponding smear (Reaction III), after estrogen therapy, is shown in Fig. 10. Note the predominance of rather large, flat epithelial cells, with clear-cut edges. A few of the cells are smaller in size and have relatively large nuclei. Compare this smear with the preliminary smear (Fig. 1).

The proliferative response to the estrogen therapy is not uniform, being more striking in some areas of the same specimen of vaginal mucosa than in others. There

is also a striking variation in the responsiveness of different individuals to the same amount of administered hormone. In some individuals 120,000 R.U. by mouth will evoke, as illustrated by Case 4, a marked regeneration of the vaginal epithelium with almost complete restoration to normal. In others the same dose produces only a very slight, patchy regeneration.

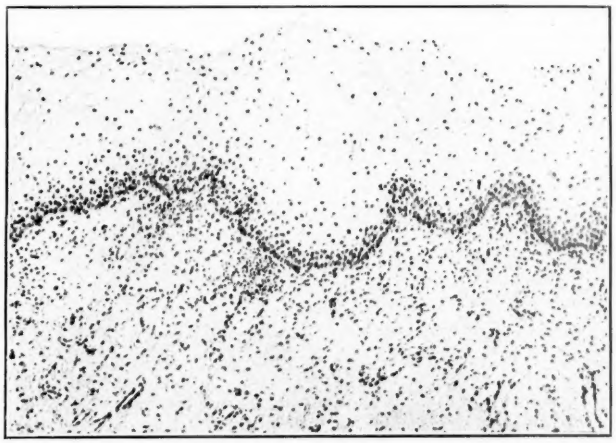


Fig. 9.—Vaginal mucosa of Case B.L., aged 54, nine years after spontaneous menopause. Biopsy taken after 120,000 R.U. estradiol (by mouth) in two weeks. Note regeneration of vaginal mucosa but absence of cornification. Compare with Fig. 5 (showing mucosa before treatment) and with Fig. 10, showing vaginal smear after treatment.

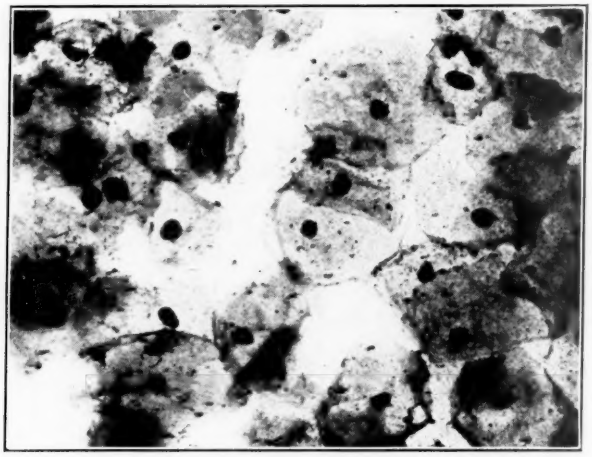


Fig. 10.—Vaginal smear taken from patient B.L., after 120,000 R.U. estradiol by mouth. Compare with pre-treatment smear (Fig. 1).

There is, furthermore, a qualitative variation in the character of the epithelial proliferation in different cases. In some cases the first evidence of reaction to the administered hormone is proliferation of the basalis and the development of 2 or 3 layers of flattened epithelial cells on the surface without actual cornification. In others, there appears to be a rapid proliferation evidenced by the marked increase in thickness of the mucosa which may be 15 to 20 cell layers deep, as illustrated in Case 4 (Fig. 10). It is noteworthy, that the vaginal mucosa after estrogen treatment is not entirely restored to a normal status. It is also of interest that in none of the cases was there any evidence of abnormal epithelial proliferation.

A very interesting fact observed in this study is the wide variations in degree of atrophy which occurred at comparable periods after cessation of menstruation. In the spontaneous menopause group, this varying tempo in the regressive process may be explained as due to the fact that although menstruation ceases, some estrogen production still continues in the ovaries for variable lengths of time. The degree of estrogen deficiency may, therefore, vary in patients after the menopause. In the case of x-ray castrates, there is probably also some residual estrogen activity in the ovaries which may vary in degree. The surgical castrates, strangely enough, also show variations in the degree of atrophy exhibited by the vaginal mucosa at similar intervals after bilateral ovariectomy. (No cases were included in this series in which there was any doubt as to the complete removal of both ovaries.) The possibility of a supernumerary ovary cannot, of course, be excluded. However, in view of the rareness of such an anomaly, this possibility need not be given serious consideration. The possibility that there may be some other source of estrogen formation in the body merits consideration.

SUMMARY AND CONCLUSIONS

1. Vaginal biopsies were taken from a group of 60 women with varying degrees of estrogen deficiency (menopause, surgical and x-ray castration). The degree of regression was compared with vaginal smears (prepared by the fuchsin method) before and after treatment with an active estrogen.

2. The vaginal smears and vaginal mucosa were classified into groups, representing various degrees of estrogen deficiency.

3. The vaginal smears according to this classification were found to correspond with graded degrees of atrophy of the vaginal mucosa.

4. After treatment with estradiol the changes in the vaginal smear reflected clearly the regenerative changes in the mucosa.

5. Atrophy of the vaginal mucosa was found in many cases not to be uniform in degree, being more marked in some areas than in others. The regenerative process resulting from estrogen administration likewise does not manifest itself uniformly.

6. Vaginal smears prepared by the fuchsin method were found to reflect the degree of regression as well as of regeneration of the vaginal mucosa in women.

7. The fuchsin vaginal smear method is recommended as a simple, reliable procedure for determining the presence of normal ovarian activity or estrogen deficiency, as well as an indicator of the efficacy of administered estrogens in cases of estrogen deficiency.

REFERENCES

(1) *Stockard, C. R., and Papanicolaou, G. N.:* Am. J. Anat. **22**: 225, 1917. (2) *Allen, E., and Doisy, E. A.:* J. A. M. A. **81**: 819, 1923. (3) *Papanicolaou, G. N.:* Am. J. Anat. **52**: 519, 1933. (4) *Papanicolaou, G. N., and Shorr, E.:* Am. J. Obst. & Gynec. **31**: 806, 1936. (5) *Salmon, U. J., and Frank, R. T.:* Proc. Soc. Exper. Biol. & Med. **33**: 612, 1936.

CHANGES IN THE UTERINE AND PLACENTAL CIRCULATIONS DURING DIFFERENT STAGES OF PREGNANCY

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IN THE American Journal of Obstetrics and Gynecology, of June, 1934, I described the anatomy and histology of the placental circulation. A review of this paper appeared in 1935. The present article is a continuation of that study and deals with pathologic changes in the placental circulation and anatomic changes in the uterine circulation during pregnancy.

CIRCULATION OF NORMAL INVOLUTED UTERUS

Injection experiments of the normal involuted uterus show that it derives its blood supply from two main sources, the uterine and ovarian arteries. The hypogastric artery gives off two branches anteriorly before entering the transverse parametrium as the uterine artery; the inferior vesicalis and the lateral umbilical artery. No branches are given off while the uterine artery traverses the parametrium. As it enters the lateral wall of the cervix, in the region of the internal os, it gives off two branches, one descending and the other ascending.

The descending branch gives off numerous fine lateral branches to the musculature of the cervix and ends in the region of the portio by anastomosis with fine vessels in the upper lateral walls of the vagina. There is no definite circular artery around the cervix. The richest blood supply of the cervix and upper vaginal wall lies laterally. The midline of these organs receives only the distal peripheral stems coming from either side.

The ascending branch of the uterine artery divides into two main branches. These penetrate a little deeper into the musculature and subdivide in dichotomous fashion as they ascend toward the fundus where a latticework arrangement of vessels is seen. The midline of the uterus receives the peripheral branches from either side, therefore it is more anemic. The main lateral fundal branches travel medial to the external longitudinal layer of muscle and they give off at right angles numerous fine, corkscrewlike branches which penetrate the oblique and internal longitudinal layers of muscle and proceed toward the superficial layer of mucosa where they end by splitting into two or more fine, hairlike stems which often appear like small glomeruli (Fig. 1).

The corkscrewlike arteries destined for the mucosa allow for easy congestion of this part because the corrugations, or substituted valves, prevent backflow when the uterus contracts and favors superficial congestion of the mucosa in the premenstrual phase. They also provide for a rapid distention of the organ, as in early pregnancy, without narrowing

their lumina. The anatomic arrangement of the uterine vascular tree is, therefore, constructed in such a manner as to accommodate for immediate functional demands whether it is during menstruation or early pregnancy. The veins in the involuted adult uterus follow the course of the arteries. The venous system, however, is less corrugated, the anastomosis is more free, and the tendency to pass beyond the midline of the fundus is greater.

The anastomosis between the uterine and ovarian arteries is very intimate and free. The main ascending uterine branch gives off two branches toward the tube on either side. The larger one pierces the outer muscle layer of the uterus about 2 cm. below the isthmus of the tube and extends laterally toward the hilus of the ovary. The other, finer branch extends from the cornu of the uterus into the tubal musculature. In the

Fig. 1.—A celloidin injection of a normal involuted multiparous uterus. The artery and vein on the left side were injected. Artery on right side alone injected. With a hand lens one can easily see the corrugation in the transverse portions and the splitting in the terminal arterioles.

region of the hilus of the ovary, there is a very rich anastomosis between the uterine and ovarian arteries. There appears to be an equal number of branches coming from the uterine as from the ovarian branch. Injection of the uterine artery alone proves this by showing a rich blood supply to the ovary, whereas injection of the ovarian artery alone shows a less reciprocal flow toward the uterus as did the uterine artery toward the ovary. From this conjointly formed, rich anastomosis in the hilus of the ovary, numerous parallel perpendicular branches enter the hilus in enormous numbers and appear as corrugated stems. This anatomic arrangement should favor congestion of the ovary, especially in the region of the developing corpus luteum, because numerous branches are attracted toward this area.

CIRCULATION OF THE PREGNANT UTERUS

Is the circulation of the pregnant uterus similarly constructed to that of the nonpregnant one? I was successful in getting the most minute

details from a celloidin injection of an eight weeks' normal pregnant uterus which was injected by way of the aorta immediately after the death of the mother. Following the injection, the pelvic organs were removed and the uterus placed in running water for twenty-four hours to remove all traces of acetone. It was then opened down the midline anteriorly and the placenta was seen attached to the upper posterior fundal wall. The ovum was removed intact. Red celloidin, representing the maternal arterial circulation to the placenta, was found in the intervillous spaces of the placenta. This shows that there is an easy flow of blood into the intervillous spaces at this time of gestation. The musculature of the uterus was carefully corroded away by hydrochloric acid and a perfect cast of the uterine circulation remained (Fig. 2).

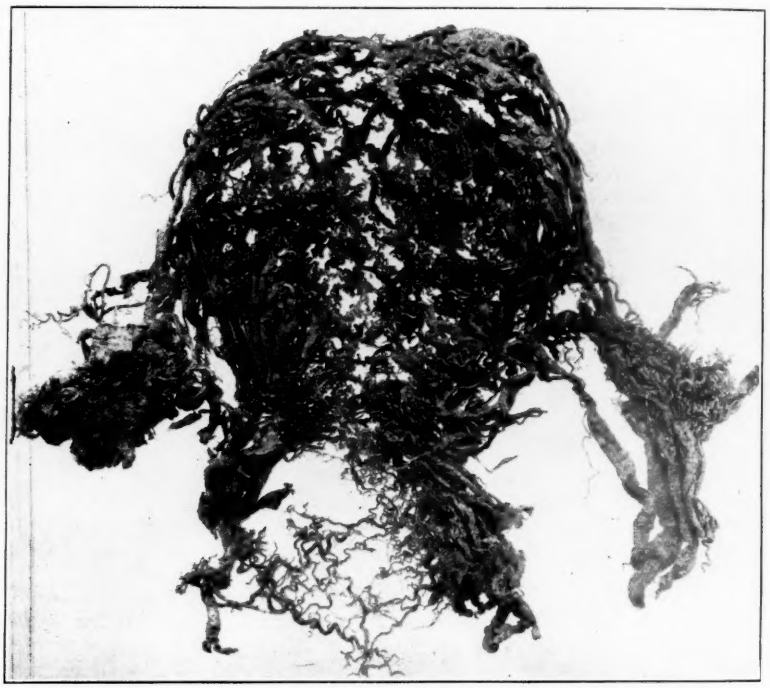

Fig. 2.—Celloidin injection of an eight weeks' pregnant uterus. Uterine arteries and veins injected. Note the uniform increase in new vessels to all parts of the uterus, including the cervix, and also to the vagina, broad ligament, and ovaries. The fine corrugations seen in Fig. 1 are retained in pregnancy.

The changes in the vascular arrangement of the uterus incident to an eight weeks' pregnancy are:

1. An increase in the number of newly constructed vessels. This is clearly shown in the fundus of the uterus, the lower uterine segment, cervix, the upper part of the vagina, and in the corpus luteum region of the ovary.

2. Instead of two main branches arising from the ascending branch of the uterine artery there are now nine vessels, some of which are elongated and enlarged tributaries of the two main vessels. As in the nonpregnant

uterus, these branches are given off in dichotomous, palmlike fashion and extend like a canopy over the fundus, but not going beyond the midline of the organ. The arteries, for a considerable distance proximal to their endings, are corrugated, especially the transverse ones.

Examining the interior of the cast (Fig. 2) one notices innumerable transverse, corkscrewlike vessels going to all regions of the decidua vera. In the region of the decidua basalis there is a greater number of similarly arranged vessels. Here they are running in parallel rows, are larger and longer than those in the decidua vera, and are in advance of the veins. One can easily understand, from examining such a cast, how easily a uterus bleeds when traumatized by abortion, and how extensive and rapid the spread of infection would be.

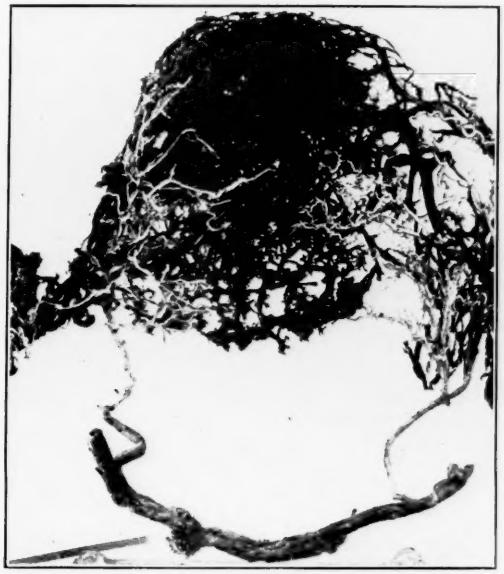

Fig. 3.—Celloidin injection of a seven months' pregnant uterus. Note the decrease in the number of vessels to the placenta-free side of the uterus and the relative increase in the number of sinuses below the placental site.

UTERINE CIRCULATION AT THE SEVENTH MONTH OF PREGNANCY

The uterine circulation at seven months' pregnancy, as shown by celloidin cast (Fig. 3) shows a marked anatomic change over that of the two months' gestation. The concentration of blood sinuses to the placental site region is pronounced. The placenta-free wall of the uterus shows atrophy of fine vessels and only a few coarse arteries with their corresponding veins are seen. The arteries still retain their corkscrewlike arrangement but are larger, more direct in their course, and less in number than the two months' pregnancy. The arteries of the tube and corpus luteum of the ovary are also larger, coarser, and show disappearance of their finer branches.

A close observation with a hand lens of the vessels and sinuses in the placental site region shows numerous interesting points. A relative increase in the thickness of the vascular area is seen. The blood sinuses are arranged in a definite anatomic way. The outer sinuses are flat and lie parallel to the surface. These represent the blood sinuses in the external longitudinal layer. The middle strata have numerous irregularly placed, oblique and transverse sinuses which form a spongelike layer. These sinuses lie between the internal and external longitudinal layers of the uterus. The inner layer of sinuses are like those of the external layer, coarse, flat, and lie parallel with the inner surface of the uterine cavity.

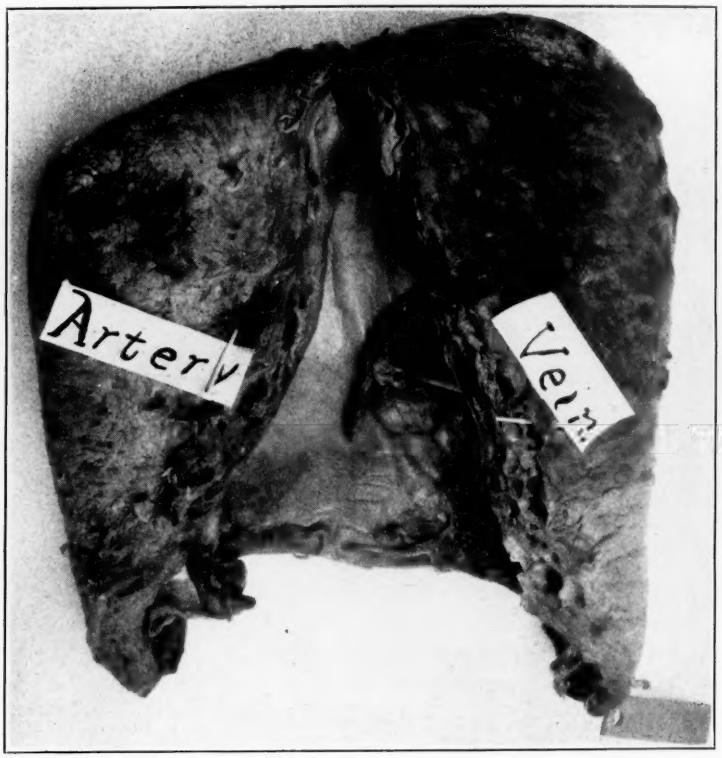

Fig. 4.—An inverted uterus. Shows the anatomical arrangement of the blood sinuses below the placental site.

In this anatomic arrangement lies the mechanism of control of hemorrhage after separation of the placenta in that the internal and external longitudinal layers of muscle and the oblique muscle fibers retract causing compression and torsion upon the sinuses in the middle layer of the uterine muscle; whereas the longitudinal parallel sinuses situated in the inner and outer longitudinal layers are only mechanically pressed upon by contraction and retraction of the longitudinal layers.

RELATION OF UTERINE SINUSES TO INTERVILLOUS SPACES

The anatomic arrangement of the blood sinuses in the uterine wall is shown in Fig. 4. This uterus was removed from a patient who had died

from cardiac disease at term. At autopsy the cervix was manually dilated and the fetus extracted. The autopsy table was then put in the extreme Trendelenburg position and the uterus was filled with water. The cervix was sewed over tightly and the uterus was removed intact and suspended in 10 per cent formalin for a week. It was then incised through the anterior surface, passing through the placental site, and the placenta pushed inward. The uterus was then inverted in order to bring the sinuses closer to the surface when mounted.

With the aid of a high power hand lens one notices that the sinuses are not seen beyond the placental site region, and that the larger, elliptical and oblique sinuses lie for the most part between the internal and external longitudinal layers of muscle. These longitudinal contracting muscle layers are less pronounced as the cervix is approached. This explains why hemorrhage is more difficult to control when the placenta is situated low in the uterine cavity.

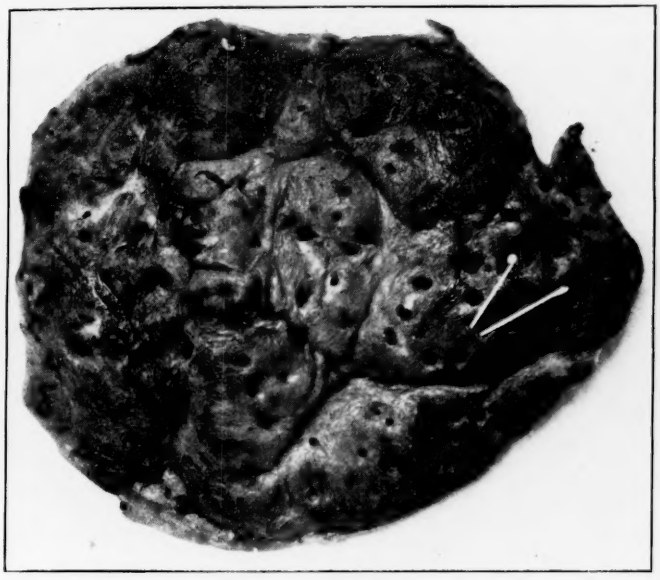

Fig. 5.—Maternal surface of normal full-term placenta showing the small fenestrae which represent the terminal portions of the spongiosa vessels which end in the decidua basalis.

It is interesting to note that into these arterial and venous sinuses are seen numerous small entrances having much the same architecture as the coronary vessels entering into the sinus of Valsalva of the aorta. These can be traced deeply into the musculature of the uterus and represent nutritional vessels to the uterus itself.

The blood in the venous sinuses is made venous from two sources: one from the intervillous spaces of the placenta, and the other from the returning deoxygenated blood from the uterine muscle itself. The most interesting point to me was the size and irregularity of shape of these sinuses, and that thrombosis did not occur more frequently. The uterine contractions must help to keep the blood flow onward. Thrombosis of

these venous sinuses frequently occurs, but the thrombus cannot easily get away into the general circulation because of the anatomic arrangement of the in-going and out-going narrow vessels which traverse the internal and external layers of uterine muscle.

Where does the maternal endothelium end in the placenta? Fig. 5 shows a placenta which was specially treated to show this. The placenta, when expressed, was immersed in warm saline. With the aid of a high power hand lens small openings were seen in the decidua basalis portion of the placenta. These openings were packed with small pieces of gauze and the placenta immersed in 10 per cent formalin for a week. The pieces of gauze were then removed. The specimen shows the terminal portions of the spongiosa vessels ending in the decidua basalis. Microscopic study of sections taken through these areas show that maternal endothelium does not line any portion of the intervillous spaces.

These small maternal vessels, or channels, in the decidua basalis are more narrow than those in the spongiosa. This hour-glass effect of the vessels through the decidua favors congestion in the intervillous spaces. This arrangement also tends to prevent blood clots, when formed in the intervillous spaces, from escaping into the general circulation.

CIRCULATORY CHANGES IN PLACENTAL VESSELS

In the placenta is a vast, fine circulatory bed susceptible to toxic or bacterial stimuli. Ricker's theory of inflammation can be applied here. In the early stages of infection of the placenta there is a primary constriction of the villous vessels, later followed by dilatation proportionate to the degree of inflammation present. This is shown by section study and injection experiments.

In rapidly produced toxemias a congestion is seen in both maternal sinuses and in villous vessels. In milder forms of toxemias there appears to be a primary constriction of villous vessels; but in stronger, rapidly produced toxemias, there is a permanent dilatation and congestion in these vessels. This permanent dilatation of vessels leads to structural changes in the walls by producing an active proliferation of endothelium and connective tissue into the lumen of the villous vessels and hence finally reduces the blood flow. This constriction, or dilatation, in vessels may be local or generalized.

Eclampsia produces, in a normal placenta, marked congestion of the peripheral vascular tree, but a placenta showing marked senile or sclerotic changes before eclampsia occurs is comparatively free from involvement, because such placentas with their thick, hyperplastic vessels and marked reduction in the finer capillary bed do not react to toxic or physiologic stimuli. The true eclamptic placenta, therefore, differs from the one associated with chronic nephritis in that the latter goes on functioning in a permanently deficient manner, as is seen in the arteriosclerotic kidney. Anoxemia in the fetus during eclampsia is partly due to adverse circulatory behavior. The fetus loses large quantities of blood into the villous vessels, and this, along with slowing of the stream in the intervillous spaces, predisposes to asphyxia of the fetus (Fig. 6).

The result of such adverse circulatory behavior is interpreted in terms of stasis. Starling showed, in 1894, that in certain organs the capillaries are normally permeable to protein to such a degree that the effective osmotic pressure becomes lower than the capillary pressure, consequently the filtration of lymph through the capillary wall is constantly taking place. Stretching of the endothelium, as results from extreme degree of dilatation, allows for increased permeability, hence the colloids tend to drain off. The osmotic pressure of the human blood is about 6.5 atmospheres, the greater part being due to colloids and inorganic salts. The high colloid osmotic pressure of the blood in normal states prevents filtration edema. Stasis resulting from extreme dilatation of vessels favors increased permeability and a resulting rubrostasis, or adhesiveness of blood cells, is seen in the fine villous vessels in such states.

Fig. 6.—X-ray photograph of barium-gelatin injection of a full-term placenta removed during eclampsia. Note the marked peripheral congestion in the villous vessels. This is best shown by stereoscopic examination.

STRUCTURAL CHANGES IN PLACENTAL VESSELS

The structural changes occurring in the placental vessels have been described in terms of ageing by Fraser.[2] His experiments showed the sum total of definite orderly sequences in anatomic changes, in the construction of the organs, and their relations. A description of senile structural changes should be classified as a physiologic phenomenon and only becomes pathologic when an exaggeration in this normal physiologic sequence occurs.

The author studied structural changes in placental vessels by means of barium and celloidin injection followed in each case with numerous histologic sections stained by hematoxylin and eosin, Van Gieson, and Weigert's connective and elastic tissue stains. In order to restrict the number of photographs, only the celloidin injections will be shown in this article.

The vascular arrangement of the young placenta has already been described.[3] From the fifth month onward the placenta gradually becomes stripped of its fine peripheral branches. The fine anastomosis is missing and each half of the placenta is more dependent upon its respective cord artery. The villous vessels begin to retract, become less diffuse, and get more direct in their course. These points are clearly shown by injection of the vascular tree at different age periods.

The primary change, then, is in the villous vessels. They retract toward the center of the villus, and when this occurs Langhan's layer of epithelial cells begins to disappear. Combined Van Gieson and Weigert's stain shows an increase of connective tissue about the fine villous vessels. Elastic tissue fibrils are seen lying outside the endothelium. Finally the more distal and finer villous vessels become obliterated in one of two ways: either connective tissue grows into the lumen and obliterates it, or hyalinized connective and elastic tissue elements compress the capillary from without. The result of such changes is a gradual obliteration of the villous vessels and increased peripheral resistance is established. This causes back pressure and slowing in the stream. The result is dilatation in the arteriole at the base of the villus and finally in the subamniotic arteries. There now exists a continuous venous congestion of the placenta because gradual obliteration of the villous arterioles causes slowing in, and consequent dilatation of, the collecting venous sinuses of the villus. These changes are constant and orderly in occurrence.

According to Thoma[4] any agent which dilates a vessel wall or decreases velocity in current gives rise to increased pressure on the intima. The late result of back pressure and dilatation is hypertrophy in the arterial coats, later expressed mainly by an irregular intimal hyperplasia or sclerotic plaque along the intima. Finally the lumen is narrowed by proliferation of elastic and connective elements of the intima into the lumen, often totally obliterating it. Usually the embedded part of the subamniotic vessels shows a greater tendency to this irregular thickening of the intima.

The cause of this irregular hypertrophy in the subamniotic vessels can be easily explained by studying the anatomic changes occurring in these vessels. The large subamniotic trunks in the young placenta receive many fine, nourishing vessels which are given to them in the region of the chorionic membrane. I was able to demonstrate this point by careful injection experiments (Fig. 7).

About the fifth month of intrauterine life, the chorionic mesoderm plate begins to show a transition to fibrous tissue. This is often a rapid and extensive process. The fine vasa vasorum leading to these vessels now becomes shut off. This sets up irregular localized nutritional defects in the arterial wall which results in weakening, as is shown by irregular sacculations and puckerings in the vessels.

The response to dilatation is hypertrophy, which is in this case irregularly laid down. This produces interrupted localized areas of proliferating elastic and connective tissue; in other words, irregular sclerosis of the arteries. The picture of this sclerosis is similar to that seen in the

cord vessels. At first, there is an increase in the internal elastic tissue lamina, which is seen as wavy black bands. This is followed by hypertrophy in the external elastic tissue lamina, and finally by a rapid proliferation of connective tissue and elastic tissue elements into the lumen of the vessel, greatly reducing its caliber. Narrowing of the vessel lumen results in progressive anemia in the placenta.

Occasionally these large subamniotic vessels become totally obliterated and new collaterals or recanalization of the occluded vessel is seen. If degeneration ensues, then we see by the combined stain, masses of hyalinized elastic tissue products lying in the vessel wall. Staining with sudan III demonstrates fatty degeneration by showing fine particles of degenerated fat in the media and intima.

Fig. 7.—A celloidin injection of a normal six months' placenta. Note the thinness of the circulatory bed at this period of gestation. Under high magnification small hairlike stems are seen attached to the large subamniotic vessels.

The veins show similar changes, but not so early in the life history of the organ. The tissue response is less marked because the vein wall is less endowed with elastic and muscle tissue. A common finding, therefore, is a marked irregular permanent dilatation in the subamniotic veins.

A common accompaniment of arteriosclerosis is hyalinization. This degenerative process, however, is never very prominent in the placental vessels. Degenerating clumps of elastic and fibrous tissue products are seen lying in the intima, and from here it spreads to involve the media.

Fig. 8.—Celloidin injection of a full-term, markedly senile placenta. Note the decrease in the number of villous vessels with atrophy at the periphery. The villous vessels are more direct and coarser in arrangement.

Fig. 9.—Celloidin injection of full-term, thick, grayish placenta. Injection showed only 7 functioning tufts of vessels, yet the fetus was born alive.

In the villous vessels it appears as an edematous swelling of elastic tissue fibers outside the endothelium which presses upon and tends to obliterate the lumen of these fine vessels. Calcification occasionally follows upon hyalinization in the larger subamniotic vessels.

Hyalinization of the maternal surface of the placenta must not be mistaken for degenerative vascular changes. In this case combined Weigert, Van Gieson, hematoxylin and eosin stains show large masses of vitreous hyalinized epithelial cells and decidual tissue in and about Nitabuch's layer. The presence of such large masses of hyaline interferes with a free vascular flow toward the intervillous sinuses. Calcification frequently follows upon such hyalinized areas. Calcification of the maternal surface of the placenta, then, cannot be classified as a consequence of sclerosis occurring in the vessels.

RECONSTRUCTION IN PLACENTAL VESSELS

Preliminary injection with barium gelatin and celloidin of these placentas described histologically as senile or sclerotic shows that every vascular tree has the power to reconstruct itself if given time and if functional demands require it. This reconstruction is brought about by an orderly arrangement in its anatomic relationship. The extensive obliteration of fine villous vessels as a consequence of senile change is compensated for by the construction of new vessels which are less fine in their anastomosis, are more direct in course, and have a more simple vascular construction (Fig. 8). This allows for a quicker, more direct flow and thus compensates for a finer, more diffuse, slower flowing capillary bed, as is seen in the young placenta. This point is very clearly shown in one of my celloidin injections of the placenta where there are only 7 corallike, newly constructed tufts which did not involve over one-seventh of the placental surface, yet the fetus was born alive (Fig. 9). This placenta was easily and quickly flushed with saline, as was to be expected.

Reconstruction in the larger subamniotic vessels is less pronounced because the process of obliteration is slower. Several new collaterals are formed, or new vessels may grow within the old obliterating ones. This process is an orderly yet consistent one.

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REFERENCES

(1) *Frankl, O.:* Ber. ü. d. ges. Gynäk. u. Geburtsh. **12:** 245, 1935. (2) *Fraser, J. R.:* Am. J. Obst. & Gynec. **6:** 45, 1923. (3) *Kearns, P. J.:* Ibid. **27:** 872, 1934. (4) *Thoma, R.:* Virchows Arch. **204:** 1, 1911.

THE COMPLICATIONS ASSOCIATED WITH EXCESSIVE DEVELOPMENT OF THE HUMAN FETUS*

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INTRODUCTION

THE average weight of infants born in the United States has been found by different investigators to be about 3,390 gm. Provided the pelvis is not contracted, it is rare for infants weighing less than 4,500 gm. to give rise to dystocia due to size. It has been found, however, that delivery of an infant weighing more than 4,500 gm. is frequently attended with serious difficulties resulting in a surprisingly high fetal and maternal mortality. Since facilities for study of a large series of excessively developed fetuses were available, this analysis was undertaken to point out the possible causative factors, the complications of labor, and the injuries to the mother and child in an attempt to make possible more accurate diagnosis and adequate treatment.

A search through the literature reveals that although excessive development of the fetus has been a matter of interest for many hundreds of years, most papers do little more than report the birth of giant infants.

The record for the largest baby is claimed by a patient of Dr. Belcher[1] of Sale City, Georgia. She gave birth to a 25 pound stillborn infant. This claim has not been allowed because the physician failed to describe the type or condition of the scale on which the infant was weighed. Ortega[2] in 1891 reported the birth of a 24 pound 13 ounce Italian boy. This case also lacks proof. The largest baby whose weight was carefully verified was born at the Louise Margaret Hospital in Aldershot, England. As reported by E. L. Moss,[3] it was the patient's second pregnancy and five days before the calculated date she gave birth to a 24 pound 2 ounce stillborn infant. As far as can be determined from the literature there is no record of any infant born alive weighing more than 15 pounds. In this study of 195 cases, the greatest weight was 13 pounds 2 ounces.

The occurrence of infants weighing 4,500 gm. or more at birth is not uncommon. At the Chicago Lying-in Hospital during the years 1931 to 1939 there were 20,219 births. In this series, 195 children weighed, 4,500 gm. or more, an incidence of 0.94 per cent. Of these, 177 weighed between 4,500 and 5,000 gm.; 13 between 5,000 and 6,000 gm.; and 1 over 6,000 gm. In Europe the highest incidence, 2.2 per cent, was found by Pape[4] in Osnabruck. In Kiel, Fuchs[5] detected 1.35 per cent. Both Pflüger[6] and Zangemeister[7] report 0.58 per cent. Kishimoto[8] in Japan reports 0.4 per cent. Among a total of 24,644 births, Kaern[9] of Copenhagen found 228 infants weighing 4,500 gm. or more, an incidence of 0.92 per cent. In 23,500 consecutive deliveries at the Johns Hopkins Hospital according to Guttmacher,[10] the figure was 1.07 per cent.

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The conditions most commonly causing excessive development of the fetus are prolonged pregnancy or unusually rapid growth of the fetus during a normal period of gestation, but large parents, multiparity, advancing age, and diabetes appear to be contributory factors.

The relationship between prolonged pregnancy and large fetuses was first demonstrated by Von Winckel[11] in 1905. This study has since been confirmed by Starcke,[12] Jacoby,[13] Zangemeister,[7] and others. Schultze,[14] however, argued that what appears to be a prolonged pregnancy may be due to fertilization during the latter half of the menstrual cycle. Assuming that impregnation may occur at any time during a twenty-eight-day cycle, there could be a variation of twenty-eight days in calculation of the date of delivery. Since Knaus,[15] Ogino,[16] and others have shown that in the great majority of women, fertilization occurs between the tenth and seventeenth days following the first day of menstruation, little variation in the length of gestation is to be expected on this basis.

The length of gestation calculated from the first day of the last menstrual period was studied in 537 women by H. and F. Hotelling[17] in 1932. These were women of superior intelligence, and it was felt that reliance could be placed on the stated date of the last menstrual period. This material showed the mean duration of pregnancy to be 281 days. Of these women, 77.8 per cent delivered between the 266th and 294th days; 12.7 per cent before and 9.5 per cent after this period. Kraul[18] (1935) selected and analyzed the histories of 8,809 women in whom the menstrual cycle was twenty-eight days. He observed that, although the mean duration of pregnancy was 280 days, 13.7 per cent delivered after 294 days. After this time pregnancy may be said to be prolonged since the great majority of births occurred within two weeks of the mean (280 days). These studies demonstrate that the duration of pregnancy shows a consistent individual variation, although according to Hotelling[17] all pregnancies in the same woman are likely to be of similar length.

An analysis of 1,000 consecutive deliveries at the Chicago Lying-in Hospital from the viewpoint of relation of weight of the newborn to duration of pregnancy clearly indicates the direct relationship between average weight and average duration of pregnancy. In other words, the larger the infant, the longer the duration of pregnancy (Table I).

TABLE I. RELATION OF WEIGHT OF NEWBORN TO DURATION OF PREGNANCY (1,000 CONSECUTIVE CASES—LYING-IN HOSPITAL)

INCIDENCE PER CENT	FETAL WEIGHT	MEAN DURATION OF PREGNANCY
0.3	1,500-2,000	243.7
3.9	2,000-2,500	259.4
14.1	2,500-3,000	275.2
41.5	3,000-3,500	282.8
29.3	3,500-4,000	285.2
9.3	4,000-4,500	287.2
1.2	4,500-5,000	292.1
0.4	5,000+	298.0

Of the 195 cases in this study, 151 were found to have normal regular menstrual periods and remembered the date of the last period prior to the onset of pregnancy. Of these, 7.94 per cent delivered before 272 days; 54.9 per cent between 272 and 294 days; and 37.08 per cent after 294 days. The mean duration of pregnancy was 288 days. These figures when compared with those of Hotelling[17] and Kraul[18] for normal pregnancy demonstrate the direct relationship between prolongation of pregnancy and excessive development of the fetus (Table II).

TABLE II. DURATION OF PREGNANCY IN DAYS

(Calculated from the First Day of the Last Menstrual Period)

	LESS THAN 272	273-294	MORE THAN 294	AVERAGE DURATION OF PREGNANCY
F. and H. Hotelling 537 normal series	25.0%	65.5%	9.5%	281
L. Kraul 8809 (3,000+ gm. fetus)	15.6%	70.7%	13.7%	280
Chicago Lying-in Hospital 151 (4,500+ gm. fetus)	7.9%	54.9%	37.2%	288

It has been stated (Stander,[19] Eden[20]) that the large size of one or both parents contributes toward excessively large fetuses. According to Gregerson,[21] in Scandinavian countries where large size is considered a racial characteristic, the average birth weight of infants is 3,530 gm., while in this country, the average is stated to be 3,390 gm., a difference of 140 gm. In 137 cases of this series where the mother's weight prior to pregnancy was known, the average was 156 pounds, a figure which is considerably higher than the average weight in clinic practice. However, no predominant racial group was found.

It is generally agreed that multiparas have larger babies than primiparas. The increase is gradual, each child being slightly heavier than the previous one.

Zangemeister[7] in 1917 and Gregerson[21] in 1937 each studied a large series of cases from this standpoint and found that the birth weight of infants born to multiparas averaged 158 gm. more than those delivered by primiparas. In the present study there were 45 primiparas and 150 multiparas. The mean weight of the infants in the first group was 4,636 gm. and in the second group, 4,730 gm. Twenty-two per cent of the multiparas had given birth to five or more children. Moreover, 38 per cent stated that infants delivered in previous pregnancies weighed 9 or more pounds.

Male infants are frequently larger and heavier at birth than female infants. The average difference in a large series of normal cases is about 48 gm. In the present study of infants weighing more than 4,500 gm., there is a marked preponderance of male (67 per cent) to female (33 per cent) infants. Unexpectedly the females averaged 58 gm. more in weight.

Advancing age is often considered a factor in the production of excessively developed fetuses. In this study the average age for multiparas was 32 years and for primiparas 27 years.

Diabetes was a very insignificant causative factor in this series, as it occurred in only two women.

PREGNANCY

No complications of pregnancy were especially associated with overdevelopment of the fetus except toxemia. This occurred in 27.3 per cent of the women in this study. Dieckmann[22] believes that large or obese women tend to have a higher blood pressure during pregnancy than women of normal size. Since these patients are above average weight it may be a contributing factor in the elevation of blood pressure.

LABOR

The course of labor in patients with excessive development of the fetus is similar to that in women with generally contracted pelves. According to Zangemeister and Lehn,[23] it is rare for normal fetuses less than 4,500 gm. in weight to give rise to dystocia. On the other hand, when the fetus is excessively developed, the frequency of complications increases in proportion to the weight. This is especially true of primiparas.

Length of Labor.—In this study the average duration of labor was 29 hours 43 minutes for primiparas and 14 hours 20 minutes for multiparas, when delivery was effected by methods other than cesarean section. Labor was prolonged to almost twice the average length for the former and about 3 hours for the latter. The mean duration of the second stage of labor for primiparas was 2 hours 47 minutes and for multiparas 1 hour.

There were a number of factors in addition to the large size of the fetus which contributed to the marked prolongation of labor in primiparas. In 19 cases the head was not engaged during the early period of labor. There were ten instances in which the occiput was in the posterior position, all persisting as such and requiring manual or forceps rotation to the anterior position before delivery could be accomplished. Secondary uterine inertia was a frequent complication.

In multiparas, labor was unduly prolonged only in association with abnormal presentations, such as transverse or breech, or when the weight of the fetus approached 5,000 or more grams. Of 22 cases with the occiput in the posterior position, 16 delivered spontaneously; 3 required manual rotation and midforceps; 2 high forceps; and 1 low forceps. Breech presentation occurred four times in multiparas and only two children survived the labor.

From this series of cases it must be concluded that the association of posterior position with excessive development of the fetus is unusually frequent, especially in primiparas, and produces serious dystocia.

TABLE III. COMPLICATIONS OF THE SECOND STAGE OF LABOR IN RELATION TO TYPE OF DELIVERY IN PRIMIPARAS

TYPE OF DELIVERY	TOTAL CASES		DÜHRSSEN'S INCISIONS		PERSISTENT OCCIPUT POSTERIOR		SHOULDER DYSTOCIA	
Spontaneous	13	28.9%	0		0		7	
Low forceps	11	24.4%	1		4		4	
Midforceps	13	28.9%	3		6		4	
High forceps	0		0		0		0	
Breech extraction	0		0		0		0	
Version and extraction	1	2.2%	0		0		0	
Craniotomy	2	4.4%	1		0		0	
Low cervical section	5	11.2%	0		0		0	
Porro cesarean	0		0		0		0	
Total	45	100.0%	5	11.1%	10	22.2%	15	33.3%

Method of Delivery (Tables III and IV).—Mechanical intervention, including cesarean section, was necessary in 44 per cent of the cases in this series, while the average for the Chicago Lying-in Hospital is 30.4 per cent. The incidence of intervention was almost twice as great in primiparas (71 per cent) as in multiparas (37 per cent).

Forceps: The usual indications for low and midforceps both in primiparas and multiparas were lack of progress and prolongation of the second stage of labor. The large fetal head, the frequency of persistent occiput posterior positions, and maternal exhaustion were responsible for this. Abnormality of fetal heart tones was occasionally the indication for intervention.

In primiparas forceps were used in 24 (53 per cent) of the cases, 28 per cent being difficult midforceps. In primiparas the average incidence for midforceps at the

TABLE IV. COMPLICATIONS OF THE SECOND STAGE OF LABOR IN RELATION TO TYPE OF DELIVERY IN MULTIPARAS

TYPE OF DELIVERY	TOTAL CASES		DÜHRSSEN'S INCISIONS		PERSISTENT OCCIPUT POSTERIOR		SHOULDER DYSTOCIA	
Spontaneous	95	63.3%	0		0		20	
Low forceps	12	8.0%	0		1		3	
Midforceps	5	3.3%	1		3		3	
High forceps	6	4.0%	2		2		3	
Breech extraction	4	2.7%	0		0		2	
Version and extraction	2	1.4%	0		0		0	
Craniotomy	5	3.3%	0		0		0	
Low cervical cesarean	18	12.0%	0		0		0	
Porro cesarean	3	2.0%	0		0		0	
Total	150	100.0%	3	2.0%	6	4.0%	31	20.6%

Chicago Lying-in Hospital is 4.6 per cent. Dührssen's incisions were necessary in five instances; the average duration of labor prior to this operation was 55 hours. Maternal exhaustion, intra-partum infection, and failure of labor to progress after 12 or more hours with the cervix in all cases dilated 6 cm. or more were the main indications.

In multiparas forceps delivery was necessary in 23 or 15 per cent of the cases. There were 5 midforceps, 6 high forceps, and 12 low forceps operations. Dührssen's incisions were done in three instances. The indications for interference here were essentially the same as for primiparas. Where high forceps was done the average duration of the second stage of labor was two hours and ten minutes. In two cases the head persisted in the occipitoposterior position. The average size of the infant was 4,930 gm. and great difficulty was encountered with the shoulders. Despite these complications all of the infants delivered by high forceps survived.

Breech Extraction: Breech presentation was present in 4 multiparas and 1 primipara, a total of 2.5 per cent of the cases (the average for the hospital is 4.0 per cent). The 1 primipara was delivered by cesarean section. Excessive development of the fetus was the indication. Labor was not unusually prolonged in the multiparas, but in each great difficulty was encountered during delivery of the shoulders and head. In two of the 4 cases the fetuses died during delivery.

Version and Extraction: Version and extraction was done in three cases, 2 in multiparas and 1 in a primipara. In the primipara the head failed to engage after a prolonged labor. Following the version it was impossible to deliver the head without craniotomy. In the multiparas, version and extraction was done in one case because of a transverse presentation and in the other after attempts to deliver the infant with forceps had failed. Both infants lived.

Craniotomy: It was found necessary to perform craniotomy in 7 cases; 2 in primiparas and 5 in multiparas, a percentage incidence of 3.6, the average for the hospital clinic being 0.6 per cent. Three of the infants had succumbed before the onset of labor and the other four died during labor before the destructive operation was performed.

Cesarean Section: The incidence of cesarean section was 13.4 per cent, approximately two and one-half times the average (5.8 per cent) at the Chicago Lying-in Hospital. Twenty-one were done in multiparas and 5 in primiparas, an incidence of 14 per cent and 11 per cent, respectively. Table V shows the several indications for this operation.

In primiparas there were two elective cesarean sections. The indication for one was a funnel pelvis with the fetus in a breech presentation, and for the other a generally contracted pelvis with disproportion between the head and inlet. One woman with a contracted pelvis was given an eight hour test of labor during which period the head failed to engage. There were two women with normal pelves who went into labor spontaneously, head not engaged but with no demonstrable disproportion. Following labors of twenty and twenty-seven hours, respectively, engagement failed to take place and low cervical cesarean sections were done. Apparently

TABLE V. INDICATIONS FOR CESAREAN SECTION

	PRIMIPARAS	MULTIPARAS
Low Cervical Section:		
Contracted pelvis, elective	2	1
Contracted pelvis, elective, repeat		3
Contracted pelvis, test of labor	1	4
Normal pelvis, test of labor	2	4
Normal pelvis, elective, repeat		3
Sterilization		3
Porro Cesarean:		
Ruptured uterus (old cesarean scar)		1
Intra-partum infection (face presentation)		1
Threatened rupture (aged 45, para xii)		1
Total	5	21

in the latter cases the excessive size of the fetus was not recognized as the cause of the failure of the head to engage or the patient would probably have been subjected to a much shorter test of labor.

In multiparas, 4 elective cesarean sections were done because of contracted pelves. Three of these had had previous cesarean operations. In 4 women with contracted pelves where cesarean section was done after a test of labor, the patients had previously given birth to large stillborn infants. The average duration of labor prior to operation in these cases was fifteen hours. In the group of 4 multiparas with normal pelves who were in labor prior to cesarean section, all had delivered one or more normal-sized infants through the birth canal without unusual difficulty. The average duration of labor in this group before cesarean section was performed was nineteen hours. The membranes had been ruptured for six or more hours and the head had failed to engage. In the latter group the average size of the infant was 4,790 gm. These examples make it apparent that a normal pelvis may occasionally be inadequate for the noninjurious delivery of an excessively developed fetus. There were no fetal or maternal deaths in the patients delivered by low cervical cesarean section.

It was found necessary to remove the uterus during cesarean operations in 3 multiparas. The indications for one was a ruptured uterus, the rupture taking place through the scar of a previous classical cesarean section. The mother lived but the infant was stillborn. The indication for the second operation was threatened rupture of the uterus in a 45-year-old multipara, having her twelfth full-term pregnancy. In the third case there was evidence of intra-partum infection, a face presentation, and failure of the cervix to dilate after twenty-six hours of irregular pains.

Perineal Injury: The complications associated with delivery were frequent. Despite the fact that episiotomy was done in 114 of the 168 patients delivered through the birth canal, there were three third degree tears, many instances of deep extension of the perineal incision, and extensive vaginal ruptures. Lacerations of the cervix were severe enough to produce bleeding and require repair in twelve cases.

Shoulder Dystocia: Frequently serious difficulty was encountered with delivery of the shoulders. Of 168 deliveries through the vaginal canal, 46 or 27 per cent of the cases were associated with shoulder dystocia. The average shoulder circumference in this group was 39 cm., 5 cm. larger than that of normal-sized infants. In at least 2 cases this complication was responsible for death of the fetus. In 7 cases undue traction on the head or pressure in the axilla produced serious injuries to the brachial plexus. Delivery of the shoulders was accomplished by a combination of methods: pressure on the anterior shoulder above the symphysis, twisting the shoulders into the transverse or oblique diameters of the pelvic inlet, or bringing down the posterior arm and shoulder into the hollow of the sacrum. In one case it was necessary to use a blunt hook in the posterior axilla in order to effect delivery of the shoulders.

Third Stage of Labor: The third stage of labor was frequently complicated by retention of the placenta and atony of the uterine muscle. Of 169 patients delivered through the birth canal, 35 (18 per cent) developed post-partum hemorrhage, 16 per cent occurred in spontaneous and 28 per cent in operative deliveries. The average incidence of post-partum hemorrhage at the Chicago Lying-in Hospital is 3.4 per cent. In 11 cases the blood loss was over 1,000 c.c. Manual removal of the placenta was necessary in 10 patients and in six the uterus was packed in order to control hemorrhage.

It is probable that in addition to the unusual stretching of the uterine muscle caused by the large fetus, prolonged labor, maternal exhaustion, and long anesthesia were additional factors responsible for the higher incidence of hemorrhage in complicated deliveries.

MORBIDITY AND MORTALITY

Maternal Morbidity: The morbidity was 30 per cent for the entire group of 195 cases studied. The increased frequency of prolonged labor, surgical intervention, and post-partum hemorrhage were probably contributing factors producing the high incidence of infection. The morbidity for spontaneous deliveries was 14 per cent while the morbidity for operative deliveries other than cesarean section was 40 per cent and for cesarean section, 77 per cent. Of the 58 morbid cases, 9 patients had severe puerperal sepsis and 2 developed femoral thrombophlebitis.

Maternal Mortality: There were 2 maternal deaths, 1 from shock and 1 from puerperal infection. The first was a 38-year-old para vii who was admitted to the Chicago Lying-in Hospital with a history of prolonged labor and intra-partum infection. Examination showed the cervix fully dilated, head not engaged, and the fetal heart was not heard. A diagnosis of intra-partum death of the fetus was made and a craniotomy was performed. The patient went into shock and died forty minutes following delivery. Autopsy permission could not be obtained. The fetus without cranial contents weighed 5,140 gm.

The second death occurred in a 24-year-old primipara who had a thirty-four-hour labor, difficult midforceps delivery, and post-partum hemorrhage. Examination of the birth canal immediately following delivery revealed a tear in the vagina extending into the right broad ligament. Hemorrhage was controlled by pack. The patient subsequently developed a severe puerperal infection and died fifty-five days following delivery. An autopsy was obtained which showed generalized peritonitis and septicemia.

TABLE VI. TIME OF INFANT AND FETAL DEATH IN RELATION TO TYPE OF DELIVERY

	ANTE PARTUM	INTRA PARTUM	NEONATAL
Spontaneous	2	1	1
Low forceps			
Midforceps		3	2
High forceps			
Breech extraction		2	
Version and extraction		1	
Craniotomy	3	4	
Low cervical cesarean			
Porro cesarean		1	
Total	5	12	3

Fetal Mortality (Table VI): The fetal mortality including both stillbirths and neonatal deaths was 10.3 per cent. For primiparas it was 13.3 per cent and for multiparas it was 9.6 per cent. The total infant and fetal death rate for the hospital among those who weighed 2,500 gm. or over is 1.9 per cent. A comparison of the two figures shows that the mortality for excessively developed fetuses is five times as great as that for all those weighing over 2,500 gm. Although this figure appears high it is lower than those given by some other writers for similar groups of cases. T. Kaern[9] who recently studied a group of 228 excessively developed infants, weighing 4,500 gm. or more, reports a fetal mortality of 14.9 per cent. Starcke[12] reports 10.5 per cent. Zangemeister[7] points out that beginning with 4,500 gm. the mortality

is directly proportional to the increase in size and weight. He states the mortality for fetuses weighing between 5,000 and 6,000 gm. is 29 per cent, for those from 6,000 to 7,000 gm. is 85 per cent, and for 7,000 gm. or over, 100 per cent.

Of 6 fetal deaths associated with maceration, 5 occurred prior to the onset of labor. Zangemeister and Lehn,[23] Kaern[9] and others report a 3 to 4 per cent incidence of ante-partum deaths in excessively developed fetuses. These authors have observed that this condition is frequently associated with excessive prolongation of pregnancy but no satisfactory explanation for cause of death can be found. In this connection the work of Snyder,[24] Koff and Davis,[25] and others, in the artificial prolongation of pregnancy in the rabbit is of interest.

They found that pregnancy could be prolonged from the normal length of thirty-two days to any desired time up to sixty days. This was accomplished by the production of fresh corpora lutea from the intravenous injection of gonadotropic hormones (Snyder[24]) or by the administration of daily doses of progesterone (Koff and Davis[25]). From the thirty-second to the thirty-sixth day each day's retention of the fetus within the uterus caused an increase in growth so that by the thirty-sixth day the average weight had increased from 55 gm. (average weight when labor occurs normally on the thirty-second day) to 80 gm., a net increase of 45 per cent in four days. When pregnancy was prolonged beyond the thirty-sixth day, intrauterine death of the fetuses invariably occurred and none was ever born alive. In other words, at thirty-six days the period of postmaturity compatible with survival of the fetus ends. No pathologic changes could be found to account for this phenomenon.

Other writers have ascribed ante-partum death of the postmature fetus to placental degeneration, but it is generally agreed that no consistent pathologic change is noted except calcification. It is noteworthy that in all five instances of ante-partum death of the fetus in our series the duration of pregnancy was 297 days or more.

In the nonmacerated fetuses there were four cases of intracranial hemorrhage. Of these, 3 were associated with difficult midforceps deliveries and 1 occurred during spontaneous delivery. Asphyxia was the most frequent cause of death and occurred in 11 fetuses. In 2, this was due to prolapse of the cord before the cervix was fully dilated; in 2 cases it was associated with breech extraction; and in 1 it was caused by rupture of the uterus. The others occurred during difficult forceps and shoulder deliveries.

DISCUSSION

The high incidence of difficult obstetric operations and the number of prolonged labors ultimately ended by cesarean section serve to indicate that the large size of the fetus is frequently missed or that recognition occurs too late for safety. Consequently the mother may be subjected to the risk of a major operation in the interest of the child, or the child may be sacrificed in the interest of the mother. If excessive development of the fetus could be recognized before the onset of labor, the unusually high maternal and fetal mortality could, without doubt, be reduced. Unfortunately there is no reliable sign or collection of signs by which antenatal diagnosis of abnormal size of the fetus can be definitely established except perhaps in extreme cases.

An abdomen of unusual size, when multiple pregnancy and hydramnios have been eliminated as possible causes, is the most valuable sign of an oversized fetus to the experienced obstetrician. This observation, associated with a large unengaged head and inability to impress the head into the inlet of a normal pelvis, should arouse suspicions that the fetus is abnormally large. In multiparas a history of the delivery of one or more large children is of importance. If one or both parents are large, if pregnancy is prolonged, and if diabetes mellitus is present in the mother, the probability of excessive development of the fetus is increased.

The presence of any of these factors should be an indication for intrauterine mensuration of the fetal head if facilities are available. Several investigators (Clifford,[26] Thoms,[27] Hodges,[28] Ball,[29] etc.) have devised methods for the measurement of the fetal skull before delivery and prediction can be made with varying degrees of accuracy as to its size. The diameter and circumference of the head are directly related to the size and weight of the fetus. Where facilities for stereoroentgenometry are available the x-ray is of inestimable value in the ante-partum diagnosis of excessive fetal size.

The obstetric management of patients who give evidence of excessive development of the fetus depends on the degree of disproportion. In patients with contracted pelves, an elective cesarean section is the method of choice. In this series of cases there were 17 patients with contracted pelves. Of the 5 delivered through the birth canal, 3 infants were stillborn. On the other hand, 12 cesarean sections were done for this indication with 1 fetal and no maternal mortality. Though the number of cases is small, the results are significant (Table VII).

TABLE VII. TYPE OF CONTRACTED PELVIS IN RELATION TO MORTALITY AND METHOD OF DELIVERY

	SIMPLE FLAT PELVIS	GENERALLY CONTRACTED PELVIS	FUNNEL PELVIS	INFANT AND FETAL MORTALITY
Spontaneous	0	0	0	0
Low forceps			1	0
Midforceps			1	1
High forceps		1		0
Craniotomy	1		1	2
Low cervical cesarean	6	4	1	0
Porro cesarean	1			1
Total	8	5	4	4

When there is doubt about the degree of disproportion, a test of labor should be given. If the head does not engage within a safe period of time, cesarean section seems to be the best method of delivery. In primiparas where the labor has a greater tendency to be prolonged and where the frequency of serious mechanical intervention and fetal mortality are higher, a shorter test of labor should be given in the interest of both the mother and the child.

In multiparas when the head is engaged or can be impressed into the pelvis, it is clear that the chance for uncomplicated delivery is good. The same holds for primiparas except for those where the head of the fetus is in the posterior position. As was pointed out earlier in this study, labors in these cases are likely to be prolonged, and the second stage is frequently complicated by failure of the head to rotate.

Stander,[19] Kaern,[9] Zangemeister,[7] and others have recommended induction of labor in cases of abnormally large fetuses. There are two main reasons for this indication. It has been shown by Zangemeister,[7] Kaern,[9] and others that chance of the child's being born alive decreases with each additional 500 gm. of weight. The danger to the fetus is mainly due to the dystocia caused by the increased weight. Moreover when pregnancy is prolonged the fetus has a greater tendency to die prior to the onset of labor than is otherwise true.

Medical induction of labor, particularly when the pregnancy is prolonged, is frequently successful. The use of Voorhees' bag in artificial rupture of membranes is not recommended, since these methods increase the incidence of infection and place the mother in great danger should more radical methods of procedure be necessary to effect delivery. It should here be stressed that induction of labor is not justifiable merely because the pregnancy has been prolonged beyond 294 days. It is only when the fetus seems excessively developed that immediate delivery should be contemplated. As a matter of fact, only one case of excessive development of the fetus occurs in every 25 pregnancies that have been prolonged beyond 294 days.

SUMMARY

Among 20,219 births at the Chicago Lying-in Hospital 0.94 per cent of the infants weighed more than 4,500 gm.

The average length of gestation calculated from the first day of the last menstrual period was 288 days for these infants.

The size of the fetus is largely dependent on the length of gestation, but size of the parents, multiparity, advancing age, or diabetes in the mother may be contributing factors in producing excessive development.

Labor presents a greater hazard for both mother and offspring when overdevelopment of the fetus has occurred.

The necessity for operative interference is increased and the incidence of toxemia, of post-partum hemorrhage, of maternal morbidity, and of fetal mortality is definitely higher than when the fetus is of smaller size.

Accurate estimation of fetal size prior to delivery with consequent modification of the technique employed will decrease maternal complications and fetal mortality.

REFERENCES

(1) *Belcher, D. P.:* J. A. M. A. **16:** 950, 1916. (2) *Ortega:* Nouvelles Arch. d'Obst., p. 481, 1891. (3) *Moss, E. L.:* Brit. M. J. **2:** 643, 1922. (4) *Pape, W.:* Ztschr. f. Geburtsh. u. Gynäk. **105:** 370, 1933. (5) *Fuchs, E.:* München. med. Wchnschr., p. 1411, 1903. (6) *Pflüger:* Quoted by Kaern (footnote 9). (7) *Zangemeister, W.:* Arch. f. Gynäk. **106:** 7, 1917. (8) *Kishimoto, S.:* Jap. J. Obst. & Gynec. **20:** 197, 1937. (9) *Kaern, T.:* Acta obst. et gynec. Scandinav. **16:** 189, 1936. (10) *Guttmacher, Alan F.:* Into This Universe, New York, Viking Press, Inc., 1936. (11) *Von Winckel, F.:* Handb. der Geburtsh. **11:** 1662, 1905. (12) *Starcke, E.:* Arch. f. Gynäk. **74:** 567, 1905. (13) *Jacoby, A.:* Ibid. **74:** 536, 1905. (14) *Schultze:* Quoted by Zangemeister and Lehn (footnote 23). (15) *Knaus, H.:* Zentralbl. f. Gynäk. **53:** 2193, 1929. (16) *Ogino, K.:* Ibid. **54:** 464, 1930. (17) *Hotelling, H., and Hotelling, F.:* Am. J. Obst. & Gynec. **23:** 643, 1932. (18) *Kraul, L.:* Wien. klin. Wchnschr. **48:** 305, 1935. (19) *Stander, H. J.:* Williams Obstetrics, ed. 7, New York, 1936, D. Appleton-Century Company, Inc. (20) *Eden, T. W.:* Lancet **204:** 1199, 1923. (21) *Gregerson, N. F.:* Acta obst. et gynec. Scandinav. **17:** 75, 1937. (22) *Dieckmann, W. J.:* Personal communication. (23) *Zangemeister, W., and Lehn, C.:* Arch. f. Gynäk. **109:** 500, 1918. (24) *Snyder, F. F.:* Bull. Johns Hopkins Hosp. **54:** 1, 1934. (25) *Koff, A. K., and Davis, M. Edward:* Am. J. Obst. & Gynec. **34:** 26, 1937. (26) *Clifford, S. H.:* Surg. Gynec. Obst. **58:** 727, 1934. (27) *Thoms, H.:* J. A. M. A. **102:** 602, 1934. (28) *Hodges, P. C.:* Am. J. Roentgenol. **37:** 644, 1937. (29) *Ball, R. P.:* Radiog. & Clin. Photog. **11:** 11, 1935.

DISCUSSION

DR. FRANKLIN F. SNYDER.—The chief factor responsible for this abnormality of the fetus has been traced to a defect in the mechanism of labor, namely, postpone-

ment of the onset of labor beyond the usual time. The question then arises as to what brings about such alteration in the time of onset of parturition.

There is much experimental evidence that the time of emptying of the uterus is under hormonal control. For instance, in the rabbit, one may start with normal animals and superimpose a new timing mechanism upon that of normal pregnancy. Koff and Davis have done this by the injection of progesterone in rabbits near term, thus augmenting the animals' store of this material which is normally much depleted as term approaches. The onset of labor is postponed thus prolonging pregnancy.

Instead of injecting progesterone, if one induces ovulation in pregnant rabbits near term so that fresh active corpora lutea are present at full term, emptying of the uterus also fails to occur at the usual time. The fetuses are retained within the uterus as long as the new corpora lutea remain functional, and then are cast out. Since the life span of corpora lutea in the rabbit is sixteen days, the time of onset of labor would be calculated to occur at the end of the sixteen-day period. Observation shows this to be the case. Although pregnancy is prolonged, the gestation period is not altered in totally irregular fashion but follows a definite pattern, for the time of termination of pregnancy still coincides with the termination of the life span of the corpora lutea. Thus the superimposing of a new ovulation cycle upon pregnancy in rabbits, reveals the close relation between the duration of pregnancy and the duration or rhythm of the sexual cycle.

How long past term the fetuses can survive when parturition is inhibited experimentally is readily determined in rabbits. For three days past term or until the thirty-sixth day, the fetuses continue to grow until the size, weight, and conspicuous covering of hair correspond to that of newborn rabbits three days after birth. Intrauterine death occurred on the fourth day past term; i.e., at thirty-six days, although emptying of the uterus failed to occur until five days later; i.e., the forty-first day, when there was marked retrogression of the corpora lutea. It is evident that these findings lend no support to the view that the onset of labor is caused by changes in the fetus, senility of the placenta, or mechanical distention of the uterus.

In brief, excessive development of the fetus in these experiments results from changes induced in the maternal organism, which in turn alter the timing mechanism that regulates the duration of gestation. Conversely, postmature fetuses of excessive size are in themselves evidence of defect or injury of the normal mechanism controlling the onset of labor.

DR. WILLIAM J. DIECKMANN.—The authors have noted some parallelism between the size of the baby and the size of the mother, but the correlation of fetal size to stature of the father is much better, as evidenced by veterinarian studies.

Dr. Koff mentioned the use of the x-ray in determining the size of the fetus and pelvis. Unfortunately the majority of the babies are still delivered in places where the special equipment for fetal and pelvic roentgenometry is lacking. The Ahlfeld or MacDonald measurements enable the experienced doctor to determine the size of the baby with considerable accuracy. Instead of guessing the weight of the baby, I suggest that these methods be taught and used.

DR. JOHN A. C. BUSBY.—I understood Dr. Koff to say that the largest baby, born alive, of which they had found any record was slightly over 15 pounds. In view of this fact I think it would be of interest to report a baby, born alive, last week at the West Suburban Hospital that weighed 16¼ pounds. This baby is still alive and doing well.

DR. PAUL H. VAN VERST.—As far as I know, a certified scale was used in the case that Dr. Busby referred to. The baby weighed 16 pounds, 3 ounces. The mother was a multipara weighing over 200 pounds before she became pregnant and about 245 pounds at the time of delivery. She had given birth previously to two large children, the largest weighing over 11 pounds. The previous pregnancy had been terminated by version and extraction because of inertia of the uterus after complete dilatation of the cervix. Similarly this time the patient developed inertia after complete dilatation had occurred rather rapidly. The attending physician called a consultant, and they again decided to do a version and extraction, which was rather

difficult, taking about thirty-five minutes. They had a little difficulty in resuscitation, but at the present time, a week after delivery, the baby is doing very nicely. The mother immediately after delivery developed atony of the uterus with severe hemorrhage. Manual removal of the placenta was done, but bleeding continued until the uterus was packed. The mother is also now doing very well. I believe a case report will be made by the attending physicians, Drs. C. N. Vetten and J. H. Skiles.

DR. ROBERT M. GRIER.—The biggest baby we ever had at the Evanston Hospital weighed one ounce less than 14 pounds. The mother was a para iv, and she was delivered without a tear. This woman was a clinic patient and weighed 160 pounds at the start of pregnancy and the day of delivery she weighed 160 pounds, having made no gain during pregnancy.

DR. EDWARD ALLEN.—Diabetic patients have large babies. Many such babies die intrapartum or intrapuerperium, not from postmaturity or obstetric trauma or over-size, but from some other outside factor.

DR. EDWARD L. CORNELL.—For the past ten years I have tried to obtain a definition of postmaturity that will hold water. If you mean by the mature baby, one delivered after 294 days, I can cite you a case of a baby delivered after 365 days which weighed less than seven pounds. If you judge postmaturity by weight, I can cite a case of a 46-year-old primipara who went 280 days, the baby was dead and weighed 13 pounds and seven ounces, without the brains or body fluid. Postmaturity cannot be judged by the weight of the baby nor by the number of weeks the mother delivers after the last menstrual period.

I think x-ray examinations do prove of value in judging disproportion. You may have a very large baby and disproportion. If these patients are given a reasonable test of labor with no progress, I think the thing to do is to deliver from above without waiting to get into difficulty. Again, if you take the relation of the size of the patient to the size of the baby as a criterion of postmaturity, I can cite you a case delivered in the old Chicago Lying-in Hospital where the baby weighed 13 pounds and 11 ounces and the mother weighed over 300 pounds.

I would not like to see a paper like this go out to the general practitioner if you base postmaturity on the number of days after the last menstrual period until delivery. If we could know the date when the patient became pregnant, then we would have something on which to base our calculations.

DR. KOFF (closing).—We agree with Dr. Dieckmann that there may be some relationship between the size of the father and that of the baby, but in a study such as this we could obtain no consistent information with respect to the size of the father.

The case described by Drs. Busby and VanVerst of the 16 pound 3 ounce baby born alive is unusually interesting, and should be reported. As far as we can determine there is no record of any infant born alive weighing more than fifteen pounds. The successful outcome should be considered a testimonial to the skill of the obstetrician, particularly since the method of delivery is by version and extraction.

We are in accordance with Dr. Cornell concerning the ambiguity of the term, postmaturity. For that very reason, we have attempted to use the term only in relationship to the duration of pregnancy. That is, when pregnancy has lasted 294 days or more. However, we wish to correct the impression that the subject of this presentation deals with prolonged pregnancy. The main purpose of this study is to point out that excessively developed fetuses frequently produce serious dystocia which results in an unusually high fetal and maternal mortality. Moreover, we feel that if a diagnosis of an abnormally large fetus can be made before the onset of labor, this mortality could undoubtedly be reduced.

It is apparent that there is some relationship between large fetuses and prolonged pregnancy. However, generally speaking, in every hundred cases of prolonged pregnancy (294 days or more), there are only four instances of excessively developed fetuses. On this basis we could hardly advocate induction of labor for prolonged pregnancy alone. On the other hand, when the fetus seems abnormally large and when the pregnancy has proceeded beyond the 294 days, it would appear to us that medical induction of labor is then indicated, particularly since in this type of case there is a 3 per cent fetal mortality prior to the onset of labor.

THE FACTOR OF ANESTHESIA IN THE PATHOGENESIS OF ASPHYXIA NEONATORUM*

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THE problem of respiratory failure in the newborn is open to a new experimental approach as a result of recent findings regarding the intrauterine origin of respiration.[1, 2] Since active respiratory movements occur throughout a large part of intrauterine life, the failure of respiration at birth must be regarded as the suppression of previous activity rather than the failure of some new mechanism to come into operation.

Investigation of the cause of depression or abolition of intrauterine respiratory movements has revealed three different types of fetal apnea, namely, acapnic, anoxemic, and anesthetic. Of these, the acapnic and anoxemic types of apnea have been described at length in a previous paper.[3] The present report is a description of the anesthetic type of apnea.

In our earliest experiments in which the rabbit fetus was observed directly through the uterine wall, a state of apnea was the characteristic finding. It was not immediately recognized that the anesthetics employed to permit laparotomy masked the normal state of activity of the fetal respiratory system. In the course of these experiments, spontaneous gasps occurred, especially when anesthesia was light. It was decided to eliminate anesthetics entirely. The technique was modified so that laparotomy could be done without resorting to narcosis. The spinal cord was sectioned in the lumbar region resulting in anesthesia of the lower abdominal area. Experiments carried out with this technique disclosed the error introduced by narcosis in the previous work and at the same time revealed the intrauterine origin of respiration. Intrauterine respiratory movements could be kept under observation for periods lasting many hours. Factors modifying the degree of activity of the fetal respiratory system were thus brought within range of experimental analysis. Starting with fetuses which were breathing at a regular rate, we were enabled now to return to the problem of the effect of anesthetics upon the fetal respiratory system and to evaluate the depressant action of various narcotic agents.[4]

METHOD AND MATERIAL

In a typical experiment, laparotomy was carried out beneath the surface of a bath of warm Ringer's solution and the gravid uterus was brought into view. In order to preserve normal circulation, care was taken to avoid exposure of the uterus to the air and to prevent mechanical stimulation. Through the thin uterine wall of the rabbit, the intrauterine respiratory movements of the fetuses were clearly ob-

*Presented at a meeting of the New York Obstetrical Society, February 8, 1938.

served. The respiratory rate of various fetuses in the litter was recorded at repeated intervals, first during a control period and later during the experimental period following administration of a given anesthetic agent. At the same time the degree of anesthesia of the maternal animal was noted. Fetuses were delivered at various intervals in order to determine the respiratory response associated with birth. Nonvolatile anesthetics were injected in solution slowly into an ear vein of the mother. Volatile anesthetics, except ether, were administered by tracheal cannula or by passage through a chamber sealed about the head of the animal. A continuous flow of the gas mixture was maintained from a Douglas bag of 100 liters capacity.

Rabbits at full term (32 days) were used throughout this work. Labor was inhibited by the injection of 1 c.c. of antuitrin-S (Parke, Davis & Co. extract of urine of pregnancy) one week before term.

Anesthesia of the lower abdomen for laparotomy was obtained by section of the spinal cord in the lumbar region.

The material upon which the present observations are based is summarized in Table I.

TABLE I. EFFECT OF ANESTHETICS UPON FETAL RESPIRATION

ANESTHETIC	APPROXIMATE DOSE	NUMBER OF ANIMALS	NUMBER OF FETUSES	SURGICAL ANESTHESIA OF MOTHER	SUPPRESSION OF INTRAUTERINE RESPIRATION OF FETUS
Pentobarbital sodium	20 mg./kg.	9	27	0	+
Morphine sulfate	5 mg./kg.	4	16	0	+
Paraldehyde	250 mg./kg.	3	5	0	+
Chloral hydrate	25 mg./kg.	2	15	0	+
Ether, open drop technique		3	8	0	+
Nitrous oxide 90% + oxygen 10%		3	10	0	+
Nitrous oxide 85% + oxygen 15%		4	15	0	0
Cyclopropane 30% + oxygen 70%		9	32	+	0

OBSERVATIONS

The present observations constitute a general survey of representative anesthetics belonging to both the volatile and nonvolatile groups. The effect of these agents upon fetal respiratory movements was determined and correlated with the depth of maternal narcosis. The amount of anesthetic was increased gradually in order to determine the point at which depression of fetal respiration occurred. The ultimate aim was to find out whether or not deep surgical anesthesia could be obtained without interruption of fetal breathing.

Nonvolatile Anesthetics.—The nonvolatile anesthetics selected for trial were pentobarbital sodium, paraldehyde, chloral hydrate, and morphine sulfate (Fig. 1). It was uniformly observed with all of these substances following intravenous administration to the mother that fetal respiratory movements were markedly depressed or completely abolished at a level of dosage well below that required to anesthetize the mother. The maternal animal remained wide awake, responsive to external stimuli and, in marked contrast to the fetus, maintained normal respiration.

The effect upon the fetus was evident within a few minutes following the injection of the mother. Under the influence of narcosis, the fetal respiratory movements may remain suppressed for hours, interrupted only occasionally by a feeble respiratory effort.

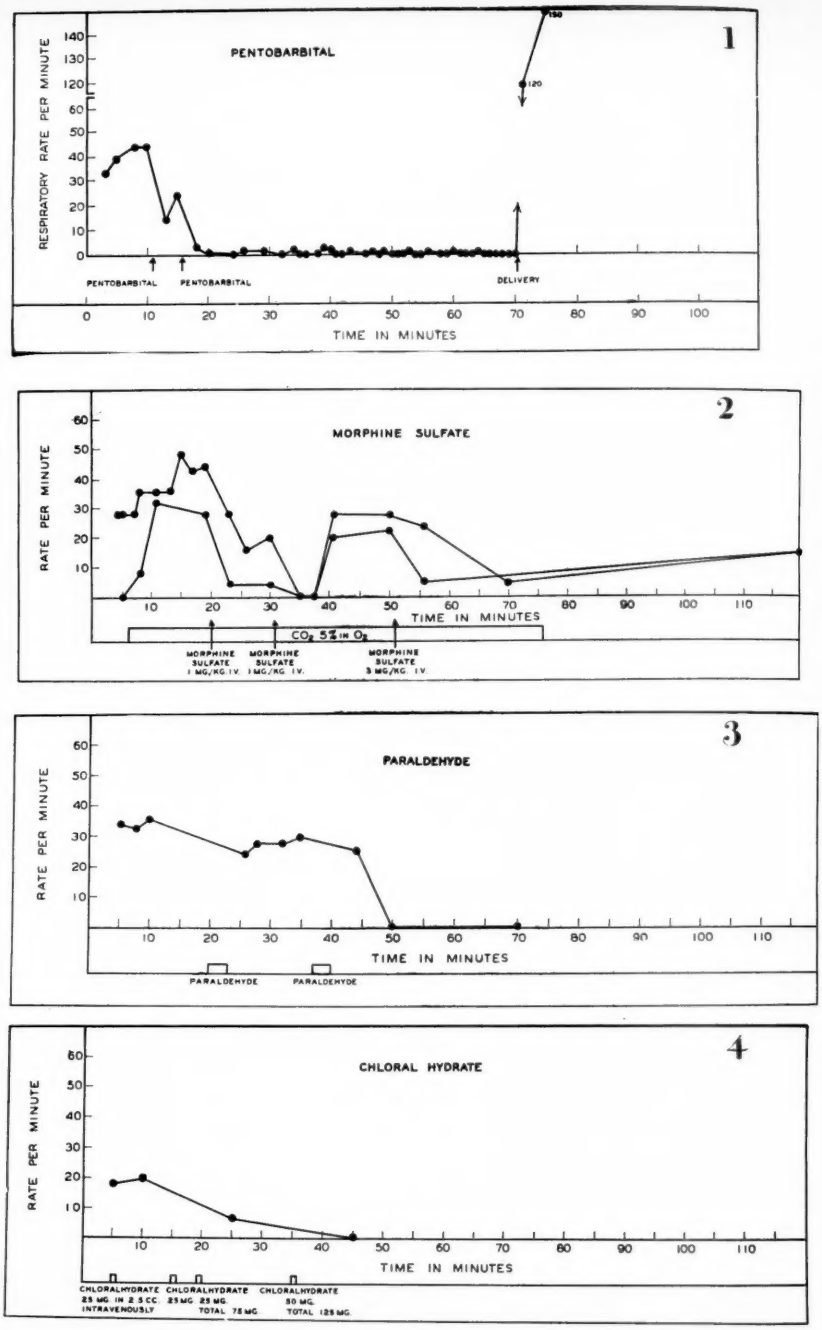

Fig. 1.*—*1*, Pentobarbital sodium 10 mg. per kg. intravenously at each injection. Mother showed little effect; reflexes active. *2*, Morphine sulfate 1 mg. per kg. intravenously at each of two injections; 3 mg. per kg. at third injection. Mother showed little effect; reflexes active. Carbon dioxide 5 per cent and oxygen 95 per cent simultaneously administered in several experiments, failed to counteract the depression of the intrauterine respiration. *3*, Paraldehyde 0.25 c.c. per kg. intravenously at each injection administered in 7 per cent solution. Mother awake, but depressed; reflexes present. *4*, Chloral hydrate 8 mg. per kg. intravenously in 1 per cent solution at each of 3 injections; 16 mg. per kg. at fourth injection. Mother awake, but depressed; reflexes present.

*The graphs illustrate the effect of anesthetics upon the fetus, as determined by changes in the rate of intrauterine respiration. The effect upon the mother at the time when fetal depression set in, is given in the following legends.

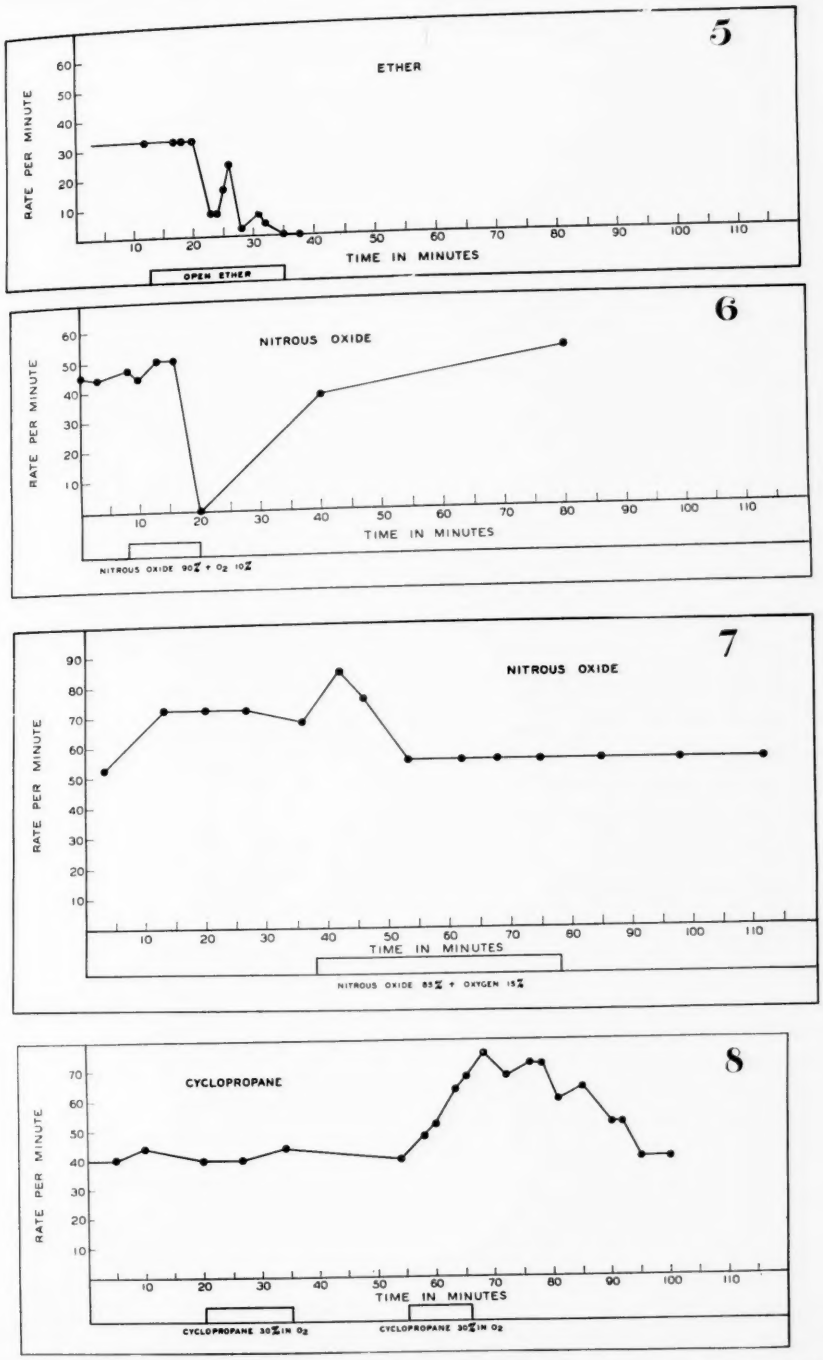

Fig. 2.—*5*, Ether by drop method. Gradual depression of fetal respiration which persisted in this instance after mother awakened from anesthesia. *6*, Nitrous oxide 90 per cent, oxygen 10 per cent. Mother depressed; corneal reflex present. *7*, Nitrous oxide 85 per cent, oxygen 15 per cent. Mother awake; reflexes active. *8*, Cyclopropane 30 per cent, oxygen 70 per cent. Mother fully anesthetized; corneal reflex lost. Deep surgical anesthesia of mother without interruption of fetal breathing.

Despite the prolonged apnea thus induced, delivery of the fetus from the uterus was promptly followed after a minimal depressant dose of anesthetic, by resumption of active respiratory movements. This indicates that the fetal respiratory system during intrauterine life is extremely sensitive to the depressant action of narcotics, but does not necessarily suffer irreversible damage. Although respiration returns following delivery and often approaches normal, evidence of narcosis is manifested by the inactivity, sluggish movements, and flaccid state of the newborn.

Volatile Anesthetics.—Of the volatile anesthetics, ether, nitrous oxide, and cyclopropane were chosen for study (Fig. 2).

When the fetuses were kept under continuous observation during the administration of open ether by the drop technique, it was found that fetal respiratory activity was gradually depressed and finally was abolished. Regular fetal respiration could not be maintained at the level of surgical anesthesia in the mother. If ether administration was terminated and the maternal animal allowed to awaken, fetal respiration often reappeared following elimination of the anesthetic.

In the experiments with nitrous oxide the results were strikingly influenced by the amount of oxygen available. Nitrous oxide 90 per cent with 10 per cent oxygen rapidly suppressed fetal respiration, although the maternal animal showed little evidence of anesthesia. In view of the depressant action of anoxemia alone,[3] it was decided to test a mixture containing a greater proportion of oxygen, namely, nitrous oxide 85 per cent with 15 per cent oxygen. This latter mixture was found to have no depressant action upon the fetus even though administered continuously over a period of forty minutes. The striking difference in the effect of these two mixtures is best explained by taking into account the relatively great difference in oxygen tension in contrast to the small change in the proportion of nitrous oxide.

The experiments with cyclopropane demonstrate that deep surgical anesthesia of the mother can be reached and maintained without interruption of intrauterine respiration. Deep anesthesia of the mother with complete loss of consciousness and disappearance of the corneal reflex persisted throughout periods of administration of the anesthetic, lasting as long as half an hour. During this time fetal respiratory movements continued uninterruptedly at a regular rate and normal depth. In many instances the rate actually increased above the pre-anesthetic level. After delivery the fetuses survived without complication, and showed none of the striking signs of narcosis, such as were previously noted in fetuses subjected to the nonvolatile anesthetics.

DISCUSSION

The fetal respiratory system during intrauterine life is peculiarly sensitive to narcosis, and the reaction to a particular anesthetic cannot be predicted from the response of the maternal animal. This special physiology of the fetus which has come to light prompts a re-examination of the anesthetics used in obstetrics, with special reference to their effect upon the fetus within the uterus. There is now available for such investigation a technique which in previous studies has aided in the elucidation of the normal physiologic regulation of intrauterine respiration.

Examination of the nonvolatile anesthetics revealed a striking depressant action upon intrauterine respiration which had not been anticipated from mere observation of the fetus after delivery or from the respiratory response of the maternal animal. Depressant effects upon the fetus are clearly revealed by this method, which might be overlooked under the usual conditions of clinical observation based upon the reaction of the mother and newborn.[4, 5] Intrauterine respiration is a sensitive

indicator which can detect the earliest effect of narcosis and permits evaluation of the extent to which a particular narcotic affects the fetus. The degree of respiratory depression may be expressed in a roughly quantitative way in terms of change in rate of fetal respiratory movements. The changes in rate were of such magnitude that conclusions could be based upon them, even though the volume changes could not be measured quantitatively.

Turning to the volatile anesthetics, experiments with ether supported the previous findings with nonvolatile agents, namely, that the fetal respiratory movements were suppressed by the time surgical anesthesia of the maternal animal was reached. In the case of nitrous oxide it was found that a high concentration of the anesthetic substance did not in itself interfere with respiration of the fetus. It was only when anoxemia was superimposed that the gas mixture, i.e., 90 per cent nitrous oxide with 10 per cent oxygen, became depressant. These mixtures likewise failed to produce surgical anesthesia of the mother without first causing abolition of fetal respiration.

Cyclopropane was selected for trial because of its high anesthetic potency, which property permits the admixture of a large proportion of oxygen, 70 per cent oxygen and 30 per cent cyclopropane being used. This mixture resulted in full surgical anesthesia of the mother and at the same time provided an abundant supply of oxygen. The results with this anesthetic agent demonstrate that one important objective of obstetric anesthesia is not beyond reach, namely, the production of full surgical anesthesia of the mother without interruption of fetal respiration.

Failure of the respiratory system to function following delivery may now be viewed in the light of factors found to be depressant to fetal respiration. Three such factors have been isolated and analyzed separately, anesthesia, anoxemia, and acapnia. Of these three possibilities, the two former, namely, anesthesia and anoxemia stand out preeminently in any attempt to explain the etiology of functional injury of the fetal respiratory mechanism. Acapnic depression, as observed in previous experiments, has been so readily reversible that there is little ground to attribute to acapnia a significant rôle in the production of permanent injury. The demonstration of the special sensitivity of the fetal respiratory system to anesthetics and anoxemia establishes the close relation of these two factors to irreversible failure of respiration.

SUMMARY

1. The problem of obstetric anesthesia has been approached by a new method, based upon the direct observation of intrauterine respiratory movements in animals.

2. Most anesthetics of both nonvolatile and volatile type suppress intrauterine respiration long before surgical anesthesia is reached in the mother.

3. The result with cyclopropane illustrates the attainment of one important objective of obstetric anesthesia, namely, the production of full surgical anesthesia of the mother without interruption of fetal respiration.

4. Because of the peculiar sensitivity of the fetal respiratory system to depression by anesthetics, the factor of anesthesia must be regarded as an important one in the pathogenesis of respiratory failure at birth.

REFERENCES

(1) *Snyder, F. F., and Rosenfeld, M.:* J. A. M. A. **108:** 1946, 1937. (2) Bonar, *B. E., and Blumenfeld:* Surg. Gynec. Obst. **66:** 179, 1938. (3) *Snyder, F. F., and Rosenfeld, M.:* Am. J. Physiol. **119:** 153, 1937. (4) *Rosenfeld, M., and Snyder, F. F.:* J. Pharmacol. & Exper. Therap. **57:** 139, 1936. (5) *Clifford, S. H., and Irving, F. C.:* Surg. Gynec. Obst. **65:** 23, 1937. (6) *Rosenfeld, M., and Snyder, F. F.:* Am. J. Physiol. **121:** 242, 1938.

CERTAIN LABORATORY FINDINGS AND INTERPRETATIONS IN ECLAMPSIA

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IN CONSIDERING laboratory tests in eclampsia, an incomplete conception of any of several factors may lead to erroneous conclusions. In interpretation, at least three questions must be borne in mind. First, what do we expect of the test; second, what are the vitiating or modifying factors which may complicate the final result; and third, what do the results mean? I can make no pretense of bringing a complete conception to the interpretation of biochemical observations. However it is not out of place to present the results of some tests in a fairly large series of eclamptic patients and to attempt to explain some of these results.

Several writers have concluded that renal function tests are of no value in toxemia of pregnancy, either because the tests have no value in predicting the later development of toxemia, or because they give normal results in toxemia. It is apparently assumed that the toxemia is either a manifestation of, or is caused by, renal deficiency. In a very recent paper, McPhail[1] writes, "It is believed that toxemia will not develop if no impairment of renal function exists." This, probably unfortunately, *is* widely believed. Many writers, however, do not accept renal insufficiency or deficiency as a cause of toxemia of pregnancy. Too much is expected of the function tests if it is thought that they may serve to predict toxemia.

As for factors modifying the tests, one might again cite the renal function measurements. The restriction of salt, commonly practiced in the treatment of toxemia, will at once reduce by nearly one-fourth the significant figures in the attainable specific gravity.[2] Or again, a tendency to oliguria is common in toxemia; in oliguria the glomerular filtration is apparently reduced,[3] and therefore most, if not all, excretion tests are modified. For instance, in oliguria the calculation of standard urea clearances gives grossly erroneous results.[4, 5] Yet there

are several papers in which low urea clearances, calculated from low urine volumes, are reported and considered as valid and typical findings in eclampsia.

What do the results of the test mean? In eclampsia many, though not all, investigators report that the blood uric acid is elevated. Some believe that this means renal retention, others that it means failure of the liver to destroy its quota of uric acid. In many eclamptics the blood nonprotein nitrogen may also rise. Some interpret this as evidence of an underlying and causative renal impairment; others think that it is caused by renal damage secondary to the toxemia. Since in oliguria glomerular filtration is diminished,[3] the rise in nonprotein nitrogen might be attributed to this factor which may be wholly independent of any renal lesion, primary or secondary.

MATERIAL AND METHODS

The present study is based upon 90 cases of eclampsia occurring from Jan. 1, 1934 to date. With very few exceptions, renal function tests were done on each patient. Blood chemistry values were obtained in patients in a postabsorptive state, except when urea clearances were done.

Uric acid of the blood was determined by Folin's last method,[6] in the Folin-Wu filtrate.

Nonprotein nitrogen of the blood was determined by Wong's method.[7]

Proteinuria was detected by the sulfosalicylic acid method. If positive, quantitative measurement was made by the procedure of MacKay.[7]

Urinary specific gravity was determined by means of a Westphal balance.[7] In the earlier cases a calibrated hydrometer was used. All readings were corrected for protein content of the urine and were discarded if sugar was present.

Volhard's urine concentration test[8] was used. The patient was given no food or fluid for seventeen hours after a 5 P.M. supper. Urine specimens were collected at 8, 9, and 10 A.M. the following morning. The specific gravity was corrected for protein content, and disregarded whenever melituria was encountered.

Urea clearances were calculated by Van Slyke's conventional formulas.[7] No results are reported in the statistics for clearances calculated from volumes of less than 25 ml. per hour.

Phenolsulphonephthalein excretion was measured at 15, 30, 60, and 120 minutes after the intravenous injection of 1 ml. of the dye.

RESULTS AND DISCUSSION

Blood Uric Acid.—Stander and Cadden,[9, 10] as well as others, have reported that in eclampsia the blood uric acid is increased; concomitantly there is little or no increase, or only a later increase, in the other nitrogenous metabolites of the blood. High blood levels of uric acid are also found when the nonprotein nitrogen rises because of renal impairment. This suggests that absolute values for the blood uric acid may not have as much significance, in toxemia of pregnancy, as would the ratio of uric acid to some other substance or group of substances. Accordingly a study has been made of the ratio between the blood uric acid and the nonprotein nitrogen. Since different methods for either uric acid or nonprotein nitrogen do not give identical values, it must be remembered that the absolute values of the ratios reported here would change with change in methods. Furthermore, uric acid itself varies more than any other nitrogenous constituent of the blood (Folin[11]). Both absolute values and ratios of uric acid to nonprotein nitrogen may therefore be expected to show considerable variation.

The relation of the blood uric acid to the nonprotein nitrogen was analyzed in 3 control series: (A) In 60 normal patients at term; (B) in 69 convalescent eclamptic patients, seven to ten days post partum; (C) in 152 blood chemistries on 27 patients

with renal impairment as shown by lowered urea clearances and often by nitrogenous retention. In the first 2 series, the blood uric acid showed no definite relation to the nonprotein nitrogen, except that in most cases the uric acid was less than 11 per cent of the nonprotein nitrogen. The low coefficients of correlation, given in Table I, merely emphasize the variability of the blood uric acid levels. The higher, and significant, correlation coefficient in the patients with renal impairment indicates that the level of blood nonprotein nitrogen should be considered when assessing the blood uric acid level, especially if the nonprotein nitrogen is somewhat elevated. Again, in this series, the ratio is usually less than 11 per cent. The statistical data are summarized in Table I. The frequency distributions of the ratios are shown in Fig. 1.

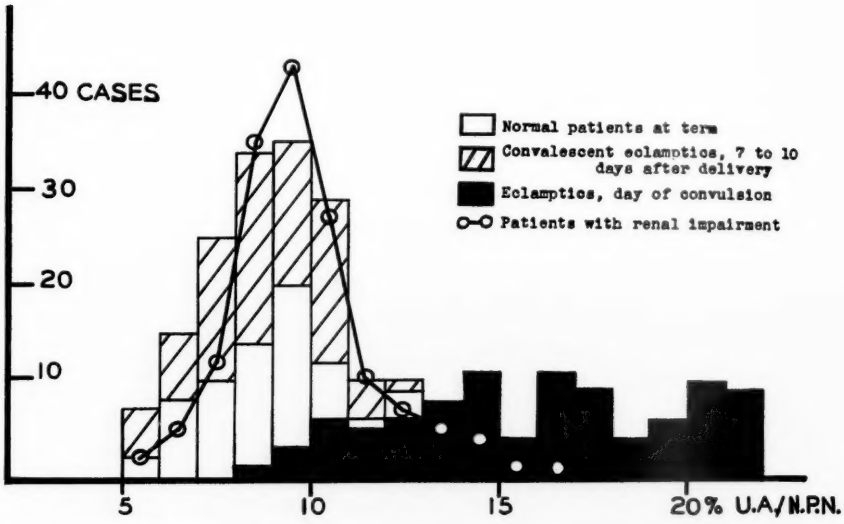

Fig. 1.—The frequency distribution of uric acid/nonprotein nitrogen ratios in the blood of eclamptic and control patients. Note that eclamptic patients show ratios characteristically above 10 per cent, while patients in the three control series show ratios usually less than 10 per cent.

Roughly then, we might take the normal proportion of uric acid to nonprotein nitrogen as about one-tenth. Accepting 10 per cent as the normal uric acid nonprotein nitrogen ratio, a blood uric acid of 4.0 mg. per cent would be of more serious import in a pre-eclamptic patient whose nonprotein nitrogen was 20 than in one whose nonprotein nitrogen was 40 mg. per cent. It is suggested that this ratio is of more significance than the absolute level of the blood uric acid. In the present series 13 of 73 eclamptic patients had blood uric acids of less than 4.0 mg. per cent on the day of convulsion, but only 4 had uric acid/nonprotein nitrogen ratios of less

TABLE I. RELATION OF THE BLOOD URIC ACID TO THE BLOOD NONPROTEIN NITROGEN IN CONTROL SERIES

GROUP	NUMBER OF PATIENTS	MEAN RATIO OF URIC ACID/N.P.N.	STANDARD DEVIATION (σ)	COEFFICIENT OF CORRELATION (ρ)	PROBABLE ERROR OF ρ
Normal	60	0.087	0.016	0.184	0.0077
Recovered eclamptics	69	0.084	0.016	0.248	0.0054
Renal impairment	27*	0.092	0.019	0.376	0.0028

*152 blood chemistries.

than 10 per cent. In Fig. 1, it may be readily seen that the uric acid/nonprotein nitrogen ratio is characteristically above 10 per cent in eclampsia.

In passing, it might be worth while to note that about half of the nonconvulsive toxemia patients observed have had elevated uric acid/nonprotein nitrogen ratios (mean 0.109, $\sigma = 0.034$). It is before the outbreak of convulsions, of course, that laboratory tests of possible premonitory significance are of the most value.

Urinary Specific Gravity.—Alving and Van Slyke[2] found that about one-fourth of the significant specific gravity of the urine was given by chloride, and that another one-fourth was attributable to urea. Chloride and urea excretion vary directly with the dietary intake of chlorides and protein, respectively. Since salt is very often, and protein sometimes, restricted in the treatment of toxemia, one might expect the urinary specific gravity in toxemia to fall short of levels otherwise attainable. Low urinary specific gravities, in eclamptic patients who have been under such dietary restrictions, cannot be interpreted as evidence of renal impairment. Furthermore the presence of edema makes effective restriction of water all but impossible. For even if water is not taken by mouth during a concentration test, the urine may still be diluted by the discharge of edema fluid.

In the present series of eclamptic patients, more than half failed to attain a specific gravity of 1.023 or higher as shown in Table II. To emphasize the dietary factor in this test, it is interesting to note that in the 33 patients on whom the concentration test was done *ante partum*, all who failed to concentrate to 1.023 or higher, had had prenatal care. Of those giving a "normal" urinary specific gravity, half had no prenatal care. In a few eclamptic patients and in many nonconvulsive toxemias, we have observed that the attainable specific gravity is highest at the time when the patient is admitted to the hospital. Under treatment, with the restriction of salt, the urinary specific gravities seen in the concentration tests, and in the morning urines, progressively decrease.

In brief, then, low urinary specific gravities in eclampsia mean little or nothing so far as the measurement of renal function, or of prognosis, is concerned.

Urea N/Nonprotein Nitrogen Ratio.—The nonprotein nitrogen of the blood is made up of many substances, some of which, chiefly urea, are excreted by the kidney, and some of which are not excreted. If there should be an impairment in the kidney's excretory function, the fraction of the blood nonprotein nitrogen which would be affected would be first and chiefly the urea nitrogen. Since the "normal" blood nonprotein nitrogen varies considerably, the ratio of urea nitrogen to nonprotein nitrogen would be a more sensitive indicator of the disturbed renal function than would the absolute level of either. Mosenthal and Hiller,[12] who advanced

TABLE II. RENAL FUNCTION TESTS IN ECLAMPSIA

RENAL FUNCTION TEST	NUMBER OF CASES	MEAN	STANDARD DEVIATION (σ)	LOWER LIMIT OF NORMAL	PERCENTAGE OF CASES IN NORMAL RANGE
Urinary specific gravity					
Ante partum	37	1.022	0.0057	1.023	46
Puerperium	82	1.020	0.0056	1.023	45
Urea N/nonprotein nitrogen					
Ante partum	25	0.407	0.088	0.40*	52
Puerperium	58	0.406	0.087	0.45*	73
Two-hour excretion of phenolsulphonephthalein					
Ante partum	18	59.2	8.20	60	56
Puerperium	29	66.9	8.75	60	76
Urea clearance					
Ante partum	19	96.7	19.7	70	85
Puerperium	64	96.8	15.3	70	98
1 year or more *post partum*	41	97.1	17.4	70	93

*Upper limit of normal.

this concept, suggested a ratio of 0.45 as the upper limit of normal. Many writers have reported a diminution of this ratio in pregnancy. In Table II are summarized the urea nitrogen/nonprotein nitrogen ratios found in the present series of eclamptic patients. Assuming an upper normal of 0.40 in pregnancy and 0.45 *post partum*, it is seen that many eclamptics fall outside of the normal limit. Perhaps this can be explained by the tendency to oliguria, or at least by the diminished urine volume output. The excretion of urea is essentially independent of the urine volume when the output exceeds 2 ml. per minute (2,880 ml. per twenty-four hours); at all lower volumes, the urea excretion diminishes as the volume falls. (These familiar facts are the basis for the calculation of maximal and standard urea clearances.) When the urine volume is 0.5 ml. per minute (720 ml. per twenty-four hours), the excretion of urea is half what it would be at a volume of 2 ml. per minute (2,880 ml. per twenty-four hours). The urea which is not excreted must, of course, be retained; this retention is physiologic and not dependent upon a renal deficiency. The retention of urea then increases the urea nitrogen/nonprotein nitrogen ratio in the blood, perhaps driving it above the arbitrarily chosen "normal" of 0.45.

It is probable that the urea nitrogen/nonprotein nitrogen is of little value in eclampsia, and that high values often would be misleading if interpreted to mean renal impairment.

Phenolsulphonephthalein.—Many of the eclamptics, as Table II demonstrates, seemed to excrete subnormal amounts of phenolsulphonephthalein. According to Stander[13] ureteral dilatation, found in about 85 per cent of pregnant patients, may become so extreme as to increase the volume capacity of the ureter to as much as 60 ml., twice the average volume output of urine per kidney per hour. While the kidney may excrete normal amounts of the dye, there will be a long lag before the excreted dye reaches the bladder. An *ante-partum* factor which magnifies the apparent reduction in dye excretion is the usual low volume of urine. If it were not for diffusion and peristalsis in the ureters, the entire two-hour excretion of dye might be retained within the ureters in many cases. With the *post-partum* diuresis, the stagnant urine in the ureters is swept out more rapidly than *ante partum*, thus accounting for the larger proportion of patients showing apparently normal excretions after delivery.

We have discarded this test as worthless in the toxemias of pregnancy.

Urea Clearance.—There is some disagreement as to the effect, if any, of normal pregnancy upon the urea clearance. Some writers, as Nice,[14] report that the clearance progressively increases as pregnancy progresses. Others, as Cantarow and Ricchiuti,[15] state that the clearance progressively decreases. In a previous paper[16] I have reviewed the literature and found that in 188 normal cases, published by 9 authors, the urea clearance averaged 101 per cent. The range was 28 to 286 per cent. However, the range is given by extreme values which represent single determinations. If perhaps half a dozen of the 188 cases be thrown out as too high or too low, the range would become the familiar one seen out of pregnancy. Dieckmann,[17] for instance, reports his own clearance as varying from 45 to 170 per cent; my own range agrees closely with this.

We conclude, therefore, that the urea clearance is unchanged in normal pregnancy. Here, as out of pregnancy, a low clearance should be checked to determine whether the low value is a normal variation or a constantly depressed level.

As Table II shows, the urea clearance in eclampsia is usually normal. Only 3 *ante-partum* and 2 *post-partum* patients (total 3 patients) of the 72 eclamptic patients who had urea clearances, showed clearances of less than 70 per cent. A one- and four-year follow-up of 2 of these patients revealed persistent hypertension, proteinuria, and constantly low urea clearances and specific gravity. The third patient had an acute pyelonephritis with her eclampsia, and within a year had returned slowly to a normal renal functional level as indicated by the urea clearance. Forty-one eclamptic patients have been followed up for periods ranging from one to five years after the eclampsia. Only 3 of these had subnormal clearances at the last, or any, observation. Two of the 3 were the patients mentioned above,

who had persistent hypertension, proteinuria and diminished renal function. The third patient's clearance, in a single determination, was 68 per cent (abnormal?).

I am not in agreement with several statements made in certain publications dealing with the urea clearance in pregnancy for reasons to be described. The mechanism of urea excretion, as shown in detail by Chasis[18] as well as by other writers with different methods, is as follows. The glomeruli of the ideal normal adult filter from the plasma a fluid volume averaging 122 ml. per minute. This ultrafiltrate is essentially identical in composition with protein-free plasma. It is remarkably constant in volume, whatever may be the final urine volume above a critical limit (see below). If all of the urea thus filtered were found in the final urine, the plasma urea clearance would be identical with the glomerular filtration, i.e., 122 ml. per minute. There is, however, an immediate and obligatory reabsorption of about 40 per cent of the filtered urea; if no more be reabsorbed, the plasma clearance of urea would then be about 73 ml. per minute. As a matter of fact, at all urine volumes above 2 ml. per minute, there is essentially no further reabsorption, and the whole blood clearance of urea averages 75 ml. per minute, the "100 per cent" of Van Slyke's maximal urea clearance. When the urine volume falls below 2 ml. per minute, a further reabsorption of urea occurs. Empirically, at these lower volumes, it has been found[7] that the urea clearance (UV/B) follows a power curve the equation for which averages

$$UV/B = 54\ \sqrt{V},$$

where U = urine urea concentration, V = volume of urine per minute, and B = whole blood urea.

Therefore the actual urea clearance, UV/B, is different at each and every urine volume below 2 ml. per minute. In order to get a *constant* which might be taken as a standard of reference, as 100 per cent, the equation is juggled, and the standard urine volume set at 1 ml. per minute, getting the form:

$$\text{Standard "Clearance"} = \frac{U\sqrt{V}}{B}$$

The result of this calculation gives what the patient's urea clearance would be if the urine volume were 1 ml. per minute. It does *not* give the actual clearance which is always UV/B. When the urine volume output falls to 0.35 ml. per minute, the urine is apparently maximally concentrated, and any further decrease in volume must be related to a parallel reversible decrease in glomerular filtration.[3]

Several investigators have reported low urea clearances in eclampsia; some have mentioned the fact that the clearances were done with low urine volumes.[17, 19] This accounts for the low clearances. For instance, in one eclamptic patient of the present series, an *ante-partum* urea clearance was done with the following result: The average minute volumes of urine were 0.182, 0.241, 1.34, and 1.86 in successive hours. The calculated standard clearances were 34, 42, 81, and 83 per cent. The first two are in error though it has been customary to calculate standard urea clearances from any urine volume below 2 ml. per minute. As mentioned above, recent work[4, 5] has shown that the assumption on which standard clearances are calculated does not obtain when the urine volume falls below 0.35 ml. per minute, and that such calculation gives results far lower than they actually should be. In the present series, all recorded clearances were calculated from urine volumes of more than 0.5 ml. per minute. Low clearances, such as are reported in the literature, could be calculated in many cases where the volume output of urine in the first hour or two of the test was below 25 ml. However the recorded clearances were obtained by continuing the test over a longer period until the volume of urine passed was satisfactory.

The statement has been made that the urea clearance in normal and in toxemic pregnancy is decreased because of the diminished urine volume.[17] So far as the actual clearance is concerned, this is true. However, in these cases, standard clearances have been calculated, and the cause assigned for low standard clearances cannot be accepted (unless the urine volume is less than 0.35 ml. per minute, in which case standard clearances must not be calculated).

It will be seen that in the equations for maximal and standard urea clearances the blood urea is the divisor. Therefore *errors in the determination* of blood urea will raise or lower the calculated clearance. *Actual variations* in the blood urea will not have this effect upon the clearance. The higher the blood urea, the more urea is filtered; of the filtered urea a constant *proportion* is reabsorbed (with correction for urine volume, discussed above). The clearance is essentially independent of the blood level of urea. Therefore the statement that edema affects the urea clearance by diluting the urea of the blood (which is in equilibrium in all of body water) cannot be accepted. Nor can another investigator's statement[20] be accepted that the urea clearance varies with the binding or release of urea by the "tissues" (unless the "tissues" are limited to the renal tubular epithelium).

In some cases of edema, there may be an oligemia (hemoconcentration) of sufficiently marked degree to diminish the renal blood flow. In such cases the glomerular filtration would probably be lowered, and extrarenally caused diminution in the urea clearance would result. In many such cases, the concomitant oliguria would point to the fallacy of calculating the standard urea clearance.

SUMMARY AND CONCLUSIONS

An analysis of some laboratory findings in 90 cases of eclampsia is presented.

In the interpretation of laboratory tests, certain modifying factors must be borne in mind. Some of these tests and their modifying factors include the following.

Blood Uric Acid.—The absolute level is often elevated in eclampsia. More generally, the ratio of uric acid to nonprotein nitrogen is increased. The upper normal ratio, by methods used here, is about 10 per cent.

Urinary Specific Gravity.—The attainable concentration of the urine is markedly reduced, not by eclampsia usually, but by the prophylaxis and treatment of the disease.

Urea N/Nonprotein Nitrogen.—This ratio varies with the urine volume output and tends to decrease in normal pregnancy. As a measure of renal function, it is nonspecific and, in toxemia especially, is unreliable.

Phenolsulphonephthalein.—In eclampsia and in pregnancy generally ureteral dilatation may be so marked that in spite of a normal renal excretion of dye, the test seems to give subnormal results. The dye may be excreted, but stagnating in the ureters, is not available for analysis.

Urea Clearance.—In my opinion, the urea clearance is unaffected in pregnancy and is normal in eclampsia, unless there is a concomitant renal disease. Urea clearances, if calculated as standard clearances, are grossly erroneous when the urine volume output falls below about 0.35 ml. per minute. The calculated standard clearance, as well as the maximal clearance, is independent of the urine volume output (above 0.35 ml./min.). It is also independent of the blood urea and of factors influencing the blood urea, such as tissue binding or tissue release of urea. When marked hemoconcentration occurs, the clearance may be low because of this extrarenal factor.

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REFERENCES

(1) *McPhail, F. L.:* J. A. M. A. **111:** 1894, 1938. (2) *Alving, A. S., and Van Slyke, D. D.:* J. Clin. Investigation **13:** 969, 1934. (3) *Chesley, L. C.:* Ibid. **17:** 591, 1938. (4) *Chesley, L. C.:* Ibid. **16:** 653, 1937. (5) *Chesley, L. C.:* Ibid. **17:** 119, 1938. (6) *Folin, O.:* J. Biol. Chem. **101:** 111, 1933. (7) *Peters, J. P., and Van Slyke, D. D.:* Quantitative Clinical Chemistry. Vol. II. Methods, Baltimore, 1932, Williams and Wilkins, pp. 527, 564, 682. (8) *Fishberg, A. M.:* Hypertension and Nephritis, ed. 3, Philadelphia, 1934, Lea and Febiger. (9) *Stander, H. J., and Cadden, J. F.:* Am. J. Obst. & Gynec. **28:** 856, 1934. (10) *Idem:* Ibid. **37:** 37, 1939. (11) *Folin, O.:* Physiol. Rev. **2:** 460, 1922. (12) *Mosenthal, H. O., and Hiller, A.:* J. Urol. **1:** 75, 1917. (13) *Stander, H. J.:* Williams Obstetrics, ed. 7, New York, 1936, Appleton-Century, p. 686. (14) *Nice, M.:* J. Clin. Investigation **14:** 575, 1935. (15) *Cantarow, A., and Ricchiuti, G.:* Arch. Int. Med. **52:** 637, 1933. (16) *Chesley, L. C.:* Surg. Gynec. Obst. **67:** 481, 1938. (17) *Dieckmann, W. J.:* Am. J. Obst. & Gynec. **29:** 472, 1935. (18) *Chasis, H.:* Cited in *Smith, H. W.:* The Physiology of the Kidney, New York, 1938, Oxford University Press. (19) *Hurwitz, D., and Ohler, W. R.:* J. Clin. Investigation **11:** 1119, 1932. (20) *Thomas, W. A., Allen, E. D., Bauer, C. P., and Freeland, M. R.:* Am. J. Obst. & Gynec. **30:** 665, 1935.

B. WELCHII INFECTIONS IN PREGNANCY*

With a Review of the Literature and a Report of Seventeen Cases

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IN 1928, Toombs and Michaelson[1] recalled attention to the problem of *B. welchii* infections in the puerperal state. Since then, a number of notable papers have appeared upon this subject in American and foreign literature. We propose to review this literature with particular reference to diagnosis and treatment, and to present a series of 17 cases occurring in our clinic.

REVIEW OF LITERATURE

The sources from which one may contract a *B. welchii* infection are manifold. Usually, this organism is found in the intestinal tract of herbivorous animals, though almost any animals, and even man, may be carriers. There are many such cases reported. The synonyms for this organism are: *B. aerogenes capsulatus, B. phlegmonis emphysematosae, B. perfringens,* and *B. welchii.* The latter term will be used throughout this paper. The nature of this infection must be diagnosed or strongly suspected, before or very shortly after the onset of its symptoms and physical signs, in order that treatment may be instituted if it is to be effective.

In 1930, Wrigley[2] promulgated certain postulates and, with a few observations concerning his first postulate, we will proceed, in the light of subsequent research, to modify all of these:

Wrigley was unable to find the *B. welchii* in the contents of the cervical canal in early labor, nor could he find it in the lochia when the pregnancy, labor, and puerperium had been normal. Falls[3] found the *B. welchii* organism in the vagina in 5.5 per cent of the 270 cases examined prenatally in 1933, while Bysshe[4] in 1938 found five positive cultures in 222 prenatal cases examined, and one positive culture in 42 cases examined on admission to the labor room. These postulates are as follows:

Postulate 1. The Organism Must Be Introduced Into the Uterus From Without, or, in rare cases, the organism already present in the vagina or cervix must be carried

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into the uterus. Typical proof of this is found in our Case 7, where we find the organism introduced by an attempted delivery in the home.

Postulate 2. Dead Tissue Must Be Present at the Time the B. Welchii Organisms Are Introduced.—Anaerobic conditions may be established by such tissue, such as a dead fetus, but more usually other injured tissue plugging the cervix. Our Case 2 exemplifies this postulate and is typical, as an arm was prolapsed for twelve hours and plugged the cervix.

Postulate 3. The Injured Tissue, or Pabulum, Must Remain in the Uterus for a Sufficient Length of Time for B. Welchii Incubation.—Typical proof of this third postulate is found in Case 8, already reported by Toombs[5] in 1932: "The membranes ruptured two days before labor started. Labor was uneventful in the first and second stages. The placenta was retained ten hours, then removed manually. The uterine cavity and vagina were packed to check hemorrhage. The pack remained in situ for twenty-six hours. Later, the case terminated in a fatal emphysema."

Postulate 4. Damaged Maternal Tissue Must Be Exposed to the Bacteria.—It has been shown[3] that the severity of the *B. welchii* infection is usually proportional to the amount of damage done to the maternal tissues. Generalized gas sepsis has been generally reported[3] in cases where there were gross manipulations in the presence of Postulates 1, 2, and 3. Our Case 1, however, is a contradictory example, for notwithstanding the presence of Postulates 1, 2, and 3, there was no resultant generalized sepsis. The dead fetus had been in utero for thirty hours, but the operative manipulations were so carried out that only a little damage was done to the maternal tissues, and our patient recovered from the mild *B. welchii* infection. At the same time, it must be remembered that the most virulent types of infection have been known to follow trivial interference. Another example is Case 13, where the gross damage to the maternal tissues should have been mild, in all probability, but was converted into a grave case with sloughing of the bladder floor and a resultant vesicovaginal and rectovaginal fistula, as the result of a pressure necrosis.

In 1900, Welch[6] classified *B. welchii* infections in pregnancy as follows: (I) Emphysema of the fetus, (II) puerperal endometritis, (III) physometra, (IV) emphysema, and (V) puerperal gas sepsis.

In 1936, Hill,[7] closely following Nurnburger and Heim, classified these infections as follows: (I) Local gas gangrene, (II) physometra or gas gangrene of the uterine wall, (III) peritonitis, and (IV) bacteriemia.

We shall classify them as follows: (I) Local gas gangrene, (II) emphysema of the uterine wall, and (III) gas sepsis: (A) general sepsis, and (B) metastatic gas gangrene.

I. LOCAL GAS GANGRENE

This class covers infections limited to either the fetus or the endometrium, or both, with or without physometra. Physometra in these cases is largely a matter of obstructed drainage and is rare when the uterus is draining well.

Falls[3] reported 6 cases of *B. welchii* infection with recovery. Four of these 6 were associated with physometra and 2 were apparently local infections which were free of signs and symptoms after delivery. Positive cultures were obtained from the fetus, uterus, and lochia in all of these cases. Hill[7] states that the majority of these cases are mild, but severe infections with hemolytic phenomena occur occasionally. Lash[8] states that if the process remains localized to the ovum or endometrium and is well walled off, the symptoms are very slight and the patient usually recovers, even though the organisms are found in the blood stream.

We present 6 cases in this group with no maternal deaths and one fetal death, which occurred in a twin pregnancy. Two of these cases were criminal abortions.

II. EMPHYSEMA OF THE UTERINE WALL WITH GAS IN THE MYOMETRIUM

It is agreed that these cases are desperate when the uterine musculature becomes involved. A fatal issue is to be expected. According to Hill,[7] "It is indeed difficult to understand how, once the uterine musculature becomes involved, recovery can occur without early extirpation of the uterus."

Uterine pain is also an outstanding feature of these cases and is vividly illustrated in Case 7, where the uterine tenderness was very marked. The actual detection of emphysema of the uterine wall is somewhat difficult as demonstrated by Case 10 of our series. One of the authors found the patient, on the day of death, with a distended abdomen and an enlarged, crepitant, boggy uterus, tender upon pressure. There was a foul lochia containing gas bubbles oozing from the vagina. No crepitation was noted in Case 8, although the uterus was large and exquisitely tender upon pressure. The uterus was removed immediately after death, and it showed a swiss cheese pattern of the cavities containing gas.

Circulatory collapse is an outstanding symptom in these cases, and is well illustrated in Case 8. The patient experienced a profound shock and recovered twenty-six hours after being packed for post-partum hemorrhage. Eighteen hours later, the patient again went into a shock from which she recovered, only to die of her sepsis two days later. Again, this phenomenon of circulatory collapse is shown well in Case 10, where the patient went into collapse two days following delivery and recovered, the blood pressure being 80/60. Another collapse occurred some six hours later, in which state she remained for four hours, then died.

Gas was demonstrated easily inside the uterine cavity and in the myometrium by a fortunate skiagram in Case 9. We have found no similar skiagram in any of the literature as far back as 1896.

Brutt and Lehmann[10] state that the uterus is enlarged, very sensitive to pressure, of a soft elastic consistency, and crepitation may or may not be found upon manipulation.

All of our emphysema cases were puerperal in character.

III. GAS SEPSIS

A. General Sepsis.—"Gas Sepsis" was used by Welch[6] to designate that important group of fatal cases in which gas bubbles are found at early autopsy in the heart, other organs, and tissues. Case 9 in our emphysematous group is comparable. Before death the skiagram revealed gas in the uterine cavity, uterine muscles, peritoneal cavity, and soft tissues in general. With the continued and repeated passage of *B. welchii* into the blood stream, clinical findings of sepsis occur. This sepsis may be associated with an endometritis, emphysema, or a peritonitis.

Case 12 is a classical example of postabortal sepsis. An initial chill occurred after an attempted abortion and the patient had a high fever the following day. Nausea, vomiting, and jaundice occurred the next day. The patient began to void dark urine. The third day after the attempted abortion, the patient was jaundiced completely, had severe headaches, intense abdominal pain and was critically ill. Catheterization removed a small amount of dark coffee-colored urine which contained albumin (4+) and hemolyzed red cells. Uterine cultures were positive for *B. welchii*. The next day, the patient rapidly grew worse, with a rapid, soft pulse, dyspnea, slow shallow respirations, deepening cyanosis, restlessness, and increased jaundice to a mahogany brown. Catheterization revealed an ounce of dark, thick, viscid material. The patient passed into a moribund state and died on the seventh day after the attempted abortion. She was mentally alert until the last day, a characteristic and striking feature. This is the classical course of gas sepsis. Case 12 (1927) is a good example of a terminal anuria when the patient seemed to be recovering from a grave infection. The entire pathologic picture was predicted before death. The microscopic examination revealed a nephritis with red blood cell casts plugging the tubules.

B. Metastatic Gas Gangrene.—Metastatic gas gangrene is usually rare and its course is rapidly fatal, with localized pain at the site of the abscess, followed by circulatory collapse, and death. Hill[7] reports one case where the abscess developed in the left buttocks upon needling and the patient died before the abscess became walled. de-Sa[11] reports a case where a previously existing tumor of the right breast became tender and hard, with crepitation developing at its base. The patient became worse, with a high fever and intense pain in the tumor. The tumor became softer

and larger and a skiagram showed an outline of the tumor and the gas which it contained. A tympanitic tumor was punctured and fetid gas escaped, but no fluid or pus. Cultures showed *B. welchii* and an anaerobic streptococci, and culture from the uterine cavity showed the same organism. The patient passed into a state of collapse and died the fourth day after admission.

We have in our series no case of metastatic gas gangrene, although Case 14 shows the result of local damage in general sepsis where both cubital fossae had local areas of tissue necrosis following intravenous injections. Metastatic cases are probably the result of the patient's lowered resistance, where the bacilli circulating in the blood stream lodge in a tumor, or in an injury with a poor blood supply and there set up an inflammatory condition. Laboratory findings, other than smears and anaerobic cultures, will give little information concerning the type of organism with which one is dealing. Anemia is the salient feature of this disease. The white blood cell count may be as low as in cases of malaria, or it may be normal, or the total may be very high with a high polymorphonuclear count. The young cells show a reticulo-endothelial increase. The hemoglobinemia may be greater than the red blood cell count would suggest, but usually it fluctuates in keeping with the total red blood cell count. The urea nitrogen and nonprotein nitrogen of the blood will be normal in cases of local infection and in some cases of general sepsis, unless the infection is superimposed upon an existing nephritis, but uremia may develop in the course of the disease. Smears for malarial parasites should be made upon all persons who live in malarial districts. The presence of a hemoglobinuria can be detected, but we have recognized this condition only in the fatal cases. Albumin is found in varying quantities but may be absent and the presence or absence is not indicative of a severe infection. The cultures of the urine are not positive for the *B. welchii* organisms in all cases. The anaerobic stool culture is seldom positive.

Since the above laboratory findings are of no particular value in dealing with the early diagnosis of the case, the anaerobic culture of the lochia and uterine contents becomes the most important medium for diagnosis. Some authors have suggested a prophylactic dose of antitoxin when the membranes have been ruptured for some time and a foul liquor or vaginal discharge is present. We do not agree with this because there would be many an unnecessary dose of antitoxin given, if this were done routinely. We strongly advise that smears and cultures be made in such cases rather than the routine which they have suggested. The insertion of a sterile speculum into the vagina under aseptic conditions will not subject the patient to undue danger, after preparation of the external os and the cervical canal, and it is not a difficult matter to obtain the intrauterine material for aerobic and anaerobic cultures. It is our belief that there will be no increased danger to the patient by this procedure. Any necrotic and foul materials plugging the cervical os can be removed with a sponge forceps for cultures and identification at this time. If the patient has a history which would suggest a rapid course of the disease, a skiagram can be made in order to detect any early emphysema of the myometrium.

DIFFERENTIAL DIAGNOSIS

The physical examination does not give much information in *B. welchii* infections because the outstanding findings are a tender lower abdomen, uterus, liver, renals, and the spleen. All these may be tender in a simple case of abortion, the patient suffering from diseases which antedate the abortion. The heart cycle and pulse rate are again of no value because there are no murmurs and no irregularities of the cycle encountered in even the more advanced types.

Peritonitis is not found in the mild cases which we classify as local infections, but it is found in those patients who suffer from a general sepsis with or without emphysema and physometra. Here again the physical findings are not characteristic of the disease itself, because the patient

may present a perforated organ. Therefore, the differential diagnosis is of great importance, positive smears and anaerobic cultures are indispensable in the early diagnosis of *B. welchii* infections.

Cyanosis is one of the common symptoms which accompany *B. welchii* infection, and it is important to differentiate between that resulting from sulfanilamide therapy or that which is seen in the later stages of eclampsia. The first sign of cyanosis is a slightly blue tint of the nails which deepens in color as the terminal state nears. A slight dusky appearance of the sclera is characteristic of all three conditions. The lips eventually become cyanotic in the moribund cases of both eclampsia and *B. welchii,* which is also the usual finding with large doses of sulfanilamide. Early edema of the lungs does not necessarily terminate fatally after the cyanosis appears, but when this condition is found, it may be the beginning of the end. There are other infections and drugs which might cause cyanosis, but the above-mentioned conditions are those encountered most often in obstetrics.

Jaundice is another finding which occurs in the more severe cases, but not in those which we have classified as local infection. Malaria is not uncommon in the South and the sclera of the eyes will be jaundiced as a result of this disease, as well as chronic infestation by certain cestodes. Of course, there may be a mixed infection with the *B. welchii,* as in Case 4, but here again, the laboratory plays a prominent part. The fulminating types of the disease which end fatally are not considered here because the bronzing of the skin is rather typical after the disease has progressed. Those different types of streptococci infections which cause destruction of the red blood cells will cause jaundice and are of importance to the obstetrician. Acute and chronic biliary diseases must not be disregarded in a jaundiced patient. However, the correct differentiation of the above conditions can be detected if a good history is available, because the jaundice accompanying a *B. welchii* infection is of short duration and deepens rapidly. This is also true when there is a calculus plugging the cystic duct.

The odor of the patient suffering from a *B. welchii* infection is not much different from that associated with typhoid. The pulse is similar in the early stages, becoming rapid and of low tension in both diseases, but it is a dicrotic pulse in typhoid fever. The patient suffering from the *B. welchii* infection has not the facies of anxiety found in the typhoid patient. The temperature is usually lower in the former disease than in the latter, and the patient suffering from a *B. welchii* infection has a cold and clammy skin in contradistinction to the hot and moist skin of the typhoid patient. Incontinence of urine and feces is a rather common finding in severe infections of *B. welchii,* with high fever, but such conditions can also result from many other causes.

Gas has not been found in the lochia of all cases but in fatal cases, only. Gas was seen in the lochia of Case 7 in the physometra group and in Case 10 in the emphysema group, but these were moribund. Gas bubbles are a rather uncommon finding in most cases, and if one waits for the presence of gas bubbles before diagnosing the condition, we believe that all efforts to save the patient will be thwarted by death.

The history of the case is most important for a differential diagnosis in any infection, but this is not easily obtained, because frequently rural patients arrive in the care of ill-informed friends and their families cannot be contacted.

The foul and discolored lochia that may be present in puerperal and abortion cases is not always due to one of those organisms classified as gas-producing bacteria, but it may be due to the anaerobic streptococci which can cause gas formation, as has been shown by some authors.[12] Here, again, the laboratory plays an important part and it is strongly suggested that smears be made from the lochia in such cases in order to classify the organisms present. One of the best methods for an early diagnosis of invading organisms is the intrauterine culture, placed upon aerobic and anaerobic media. It is true that some time has to elapse before the reports of such cultures are available, but treatment should be instituted to combat the organisms recognized in the smears.

The exact diagnosis of the infection is not always easy, as we have shown. The laboratory findings, with the valued assistance of the roentgen ray, are the final criteria for the diagnosis. This being true, upon admission to the hospital, the question of differential diagnosis between *B. welchii* and other infections, which give similar clinical findings, is of the greatest importance. All of us have seen patients die as a result of the *B. welchii*, and it is not the purpose of this paper to list all the changes and findings, because many writers have already described these conditions. But we do wish to emphasize some of the significant facts concerning the more severe cases, such as: a rapid, low-tension pulse, a sallow skin which is cold and clammy, and perhaps a normal temperature. The fulminating fatal types present dyspnea, cyanosis, consciousness to the last as a rule, and terminal restlessness. Rather, we wish to present the physical condition of a case which does not terminate fatally. The differential diagnosis becomes complicated in view of the multiple symptoms and physical findings.

TREATMENT

The treatment of this infection is varied and there is no preparation which will cure all cases. We would like to recall to you the dosage advised by Porter[13] for antitoxin. The unit is the amount of the unconcentrated antitoxin to neutralize 100 M.L.D. of welchii toxin, i.e., minimum lethal dose of toxin that will kill a 300 gm. pigeon.

The so-called specific treatment used in the United States is a polyvalent antitoxin serum, but all have witnessed the occasional failure of this preparation. Of course, if the condition is diagnosed early, massive doses of the antitoxin intramuscularly and intravenously are indicated and the infection will be confined within limits. When the *B. welchii* and its associated groups are recognized in the smears, a massive dose of serum should be given intramuscularly at that time, and an earlier diagnosis of these cases can be made if this procedure is followed. Likewise, if the streptococci are recognized in the smears, it is well to give 20 ml. of puerperal polyvalent antistreptococci serum in the same manner. It is the belief of the authors that many fatalities can be averted if this is done. Of course, the usual intradermal tests should have been made preceding the injections.

It seems that the number of units administered can be unlimited without injuring the patient, but the prophylactic dose of 10,000 international units is not sufficient to prevent further spread in even the local infections. The total dosage administered

depends upon the condition of the patient, and we suggest that massive doses be given twice each day for a few days, as soon as a positive culture or smear has been reported, and until the cultures in the media suggest that the organism is becoming attenuated.

After the patient is admitted to the hospital, she should be placed in strictest isolation. The importance of this procedure cannot be overemphasized, knowing that the organism has been cultured even from the delivery room and its contents. A mat soaked in bichloride of mercury solution and placed upon the threshold of the patient's room is of some value in these cases, but much less so than in those cases of other acute infections. All persons entering that room must wear sterile gowns and gloves. We insist upon all gowns, gloves, bedclothing, and articles in the room being sterilized by the fractional method before being returned to service. The importance of fractional sterilization cannot be overstressed, and if the diagnosis is made before the onset of labor, the patient should be delivered in a room equipped to handle infected cases. The room is closed from further use for a period of forty-eight hours upon discharging the patient from the hospital.

Oxytocics are important in all cases of a puerperal endometritis when administered in the proper dosage over a period of days. The usual routine of giving an ergot derivative for a few days is not of much value, because these patients suffer from an acute condition and the resultant effect is almost nil. Pituitary extract is the best drug to bring about proper contraction of the myometrium in endometritis, and we advise that 1 ml. be given every hour for four to five doses and then every two to three hours during the first twenty-four hours after the positive smear. In one case (Case 7), a combination of oxytocics was administered for seven days after the diagnosis was made, but it must be remembered that ergot and pituitrin do not have a synergistic action.

The diet and the fluid intake should be much greater than the minimum requirements for maintenance. The fluid intake and output should be carefully recorded every twelve hours, and the patient should receive at least 4,000 c.c. of fluids each day, the method of administering being dependent upon the condition of the patient. We recommend a low protein, salt-free diet because of the accompanying nephritis. Rapid destruction of tissues with an accumulation of nitrogenous products is readily shown by the resulting uremia in the severer types. We believe that vitamins have their place in the regimen and our patients receive concentrated vitamin preparations twice daily.

We strongly suggest the early digitalization of all patients until symptom-free, in order to increase diuresis, prevent circulatory collapse and slow the pulse, lest the patient should suffer from a severe infection later in the course of the disease. Massive doses of potassium citrate are administered early and continued until the patient is definitely free from her infection. Most diuretics can be used with the desired results. The mercurial preparations must not be used.

Acidosis is a rather constant finding in *B. welchii* infections. Originally, we used intravenous soda solutions for a rapid effect, but a much better and less dangerous preparation is Hartmann's solution when the CO_2 combining power of the blood ranges below 45 per cent. An intravenous solution of 500 c.c. will suffice and this may be repeated as often as necessary. Large doses of soda given by mouth will assist in combating this condition. We suggest two drachms every three hours if there is no protracted emesis.

The peritoneal cavity and its organs suffer from the devastation wrought by this bacillus. Marked distention of the abdomen is present in those cases where the disease has progressed beyond that point which we classify as local infection. However, we institute deflation of the intestinal tract by the insertion of tubes from above and below. The Wangensteen apparatus is inserted into the duodenum, left in situ as long as there is distention, and the patient is fed through the tube which is clamped for a couple of hours after the liquid meal. The colon tube is not allowed to remain in situ for more than two hours at a time because injury to the soft tissues may result. We attempt to treat peritonitis in the same manner, but we have not had good results and all such cases have terminated fatally.

The question of transfusions is of great importance. The rapid hemolysis of the red blood cells, which may occur in some cases, is too accelerated for the reticulo-

TABLE I

			LOCAL INFECTION						GAS SEPSIS	
			CASE 1	CASE 2	CASE 3	CASE 4	CASE 5	CASE 6	CASE 7	CASE 8
Race			White	Colored	White	White	Colored	Colored	Colored	Colored
Age			22	34	32	23	18	22	15	38
Para			2	10	7	9	0	2	0	8
Gestation			8 wk.	40 wk.	9 wk.	40 wk.	40 wk.	12 wk.	40 wk.	40 wk.
Membranes ruptured			48 hr.	32 hr.	48 hr.	4 hr.	6 hr.	Unknown	72 hr.	½ hr.
Total hr. labor			None	41 hr.	None	19¾ hr.	12¼ hr.	None	96¼ hr.	27½ hr.
Type delivery			Criminal abortion	Version	Criminal abortion	Low forceps	Midforceps	Criminal abortion	Craniotomy	Spontaneous
Temperature			98.6°-105°	99°-105°	98°-104°	98°-104°	98°-101°	98°-101°	100°-105°	98°-104°
Pulse			120	80-130	76-120	74-88	84-104	74-130	98-140	86-130
Respirations			20-22	20-30	20-26	20-22	20-22	20-24	20-26	20-22
Blood Pressure			Not reported	100/70	98/72	120/80	130/96	110/70	150/100	Not reported
Hospital days			7	17	6	28	19	12	1	4
Gas bubbles			No	No	No	No	No	No	None on Adm.	No
Cultures	Uterus	Negative	0	2	2	1	1	2	0	0
		Positive	1	1	0	1	0	0	1	1
	Blood	Negative	0	1	1	0	0	0	1	1
		Positive	0	4	1	2	2	1	0	0
Laboratory findings			R.B.C.: 3,5 Urine: Neg.	Hg.: 64-72% R.B.C.: 3,3-3,4 W.B.C.: 16,900 Urine: Casts and Alb. Malaria: Neg.	Hg.: 70% R.B.C.: 3,6 W.B.C.: 11,2 Urine: Neg. Malaria: Neg.	Hg.: 56% R.B.C.: 3,0 W.B.C.: 9,0 Urine: Neg. Malaria: Pos. Ict. index 8.	Hg.: 60-72% R.B.C.: 3,7 W.B.C.: 12,0 Urine: Neg. Malaria: Neg.	R.B.C.: 2,8-3,7 Hg.: 60-72% W.B.C.: 18,8 Urine: 10-12 Pus cells	R.B.C.: 4,3 Hg.: 80% W.B.C.: 12,0 Urine: 2+ Alb. Malaria: Neg.	R.B.C.: 1,0-3,5 W.B.C.: 36,6 Hg.: 70% Urine: Neg. Malaria: Neg.
Complications			None	Midwife used pin to rupture membranes	None	Tertian malaria	Toxemia. Atonic bladder. Infected epis.	Hemorrhage. Vag. packed. To hosp. 2 days later. Cervix necrotic. Mixed infection.	Attempted forceps by rural Doctor. Face presentation. Eclampsia—craniotomy. Peritonitis. Oliguria	Manual removal of placenta. Jaundice. Pelvic thrombosis
Result	Mother		Lived	Lived	Lived	Lived	Lived	Lived	Died	Died
	Baby		Abortion	(Twins) 1 D 1 L	Abortion	Lived	Abortion	Abortion	Died	Lived
Autopsy			None	None	None	None	None	None	Yes	Yes

		GAS SEPSIS					PHYSOMETRA AND EMPHYSEMA			
		CASE 9	CASE 10	CASE 11	CASE 12	CASE 13	CASE 14	CASE 15	CASE 16	CASE 17
Race		Colored	Colored	Colored	White	Colored	Colored	Colored	Colored	Colored
Age		36	16	32	22	22	17	38	23	32
Para		10	2	0	1	1	0	8	0	4
Gestation		40 wk.	40 wk.	36 wk.	4 wk.	40 wk.	35 wk.	40 wk.	40 wk.	40 wk.
Membranes ruptured		17 hr.	5 hr.	72 hr.	22 hr.	22 hr.	Intact on adm.	Intact on adm.	48 hr.	7 hr.
Total hr. labor		21 hr.	13¼ hr.	96 hr.	None	47¾ hr.	38 hr.	72 hr.	72 hr.	63¼ hr.
Type delivery		Postsection	Breech extraction	Evisceration	Criminal abortion	Spontaneous	Spontaneous	Not delivered	Post-section	Craniotomy
Temperature		98°	98.4°-104°	99°-101°	97°	98°-101°	99°-106°	100°-102°	Moribund	98°-102°-x6
Pulse		120	120-130	130-170	84-146	80-130	50-170	94-120	No pulse	110-120
Respirations		22	22-52	42-60	30-50	22-32	20-46	24-30	None	24-30
Blood Pressure		89/40	120/70-50/30	Not reported	90/45-80/40	110/80	200/130-120/80	150/110	20/00	90/60
Hospital days		1¾ hr.	3	3	6	60	29	2	1 hr.	12
Gas bubbles		Yes	None on Adm.	No	No	No	No	No	Yes	No
Cultures	Uterus Negative	0	0	1	0	1	2	0	0	0
	Uterus Positive	1	1	0	1	1	2	1	1	1
	Blood Negative	0	0	0	1	1	2	2	0	1
	Blood Positive	0	1	1	0	0	2	0	0	0
Laboratory findings		None	R.B.C.: 2,0-2,54 W.B.C.: 14,4 Hg.: 40-56% Urine: Neg. Malaria: Neg.	R.B.C.: 3,0 W.B.C.: 14,5 Urine: Pus, blood and alb.	R.B.C.: 1,75-2,8 W.B.C.: 16,0-48,3 Hg.: 48% N.P.N.: 247 Urine: 4+ alb., R.B.C., and pos. bac.* Malaria: Neg.	R.B.C.: 2,5-4,1 Hg.: 47-82% W.B.C.: 6,4-16,2 Urine: 4+ alb. and pos. bac.* Malaria: Neg.	R.B.C.: 2,4-3,9 W.B.C.: 11,8-12,8 Hg.: 40-64% Urine: Neg. Stool: Neg. N.P.N.: 26 Sugar: 102 Ict. Index: 10	R.B.C.: 3,25 Hg.: 62% W.B.C.: 5,4 Urine: Neg. Malaria: Neg.	Uterine smear and cultures Pos. bac.*	R.B.C.: 1,63-2,99 Hg.: 50-60% W.B.C.: 12,0 Malaria: Neg. Urine: 2+ alb. Stool: Neg.
Complications		Rural doctor attempted delivery and ruptured uterus. Gas escaped from stab wounds and exploded upon igniting	Footling. Retraction ring. Incontinence; jaundice. Mixed infection. Physometra.	Rural doctor disarticulated fetal left arm. Hysterectomy on third day. Mixed infection	General peritonitis. Uremia.	Midwife and Doctor gave 3 c.c. pituitrin as induction. Base of bladder sloughed away. Vesico-vaginal fistula. Vaginal atresia.	Eclampsia, incontinence. Jaundice. Large liver and spleen. Necrosis of cubital fossae and cervix	Epilepsy. Ruptured uterus. Dead fetus with hydrocephalus. Sudden collapse	Rural Doctor gave 3 amp. pituitrin and then used forceps	Prolonged labor. Hydrocephalus. retraction ring. Craniotomy. Crepitant abdomen. Peritonitis
Result	Mother	Died	Died	Died	Died	Lived	Lived	Died	Died	Died
	Baby	Died	Died	Died	Abortion	Died	Lived	Died	Died	Died
Autopsy		Refused	Refused	Yes	Yes	None	None	Yes	Refused	Refused

**B. welchii.*

endothelial system and the loss must be replaced with transfusions. Sulfanilamide has been used successfully in some cases, but we have had no experience in its use. It does seem logical, however, that the resulting anemia will be quite a problem to combat when rapid hemolysis is taking place as a result of the infection and the necessarily massive doses of this drug. The method used in administering the blood is not of importance, but daily transfusions are strongly urged. We believe that 300 to 500 c.c. of blood will give the patient food, cell replacement, and also have a polyvalent effect upon the organisms which so frequently complicate the disease. Perhaps better results can be obtained if these daily transfusions are continued for the same period of time as that suggested in regard to the antitoxin, and we see no objection to giving the patient a transfusion twice a day if the blood is available. The red blood cell count may be lower than the hemoglobin determination would indicate, or the reverse of this condition may be true, and the supply of available blood should be used for replacement in either condition.

We would like to stress the importance of the intrauterine cultures, and to reiterate that these should be taken upon admission, if the smears are positive for *B. welchii* or any other anaerobic organism. Repeated cultures will give an index of progress in the fight to prevent a fatal termination. This procedure is not a difficult one to perform and it should be done more often than is customary.

Potassium permanganate has been used as an intrauterine douche in combating the anaerobic streptococci, and some authors have suggested that this method be used in treating the *B. welchii* infections within the uterus, although they fear air embolism. Is it not logical to assume that, as regards air embolism, it has been preceded by the gas resulting from the infection? The senior author decided that hydrogen peroxide and 10 per cent mercurochrome would cause a gentle debridement of the necrotic materials; the liberated oxygen would destroy the anaerobes; and the mercurochrome would destroy those organisms causing the mixed infection found in the more severe cases. He suggests that these intrauterine douches be repeated at least every other day because of the spore-bearing characteristics of the *B. welchii*. Vaginal instillations with the same mixture seemed to be efficacious in the treatment of the vaginal necrosis and were given twice daily. Nine of these cases reported have been under his supervision and no operation was performed.

Incision into the peritoneal cavity for drainage has been reported with fair results. Also, a number of cases of extirpation have been reported, the results have not been particularly gratifying on the whole. We have had little experience with such procedures. Unfortunately, the routine lochial smear and intrauterine culture in criminal abortion and suspicious cases has been discontinued on our service since 1934, so that 5 fatalities have occurred since that time, with clinical findings of *B. welchii* infection. But, we are reporting the proved cases and are omitting the unknown.

TABLE II. SUMMARY

	TOTAL NO. CASES	NO. MATERNAL DEATHS	NO. FETAL DEATHS	PER CENT MORTALITY		PER CENT CORRECTED MORTALITY (LIVED)	
				MATERNAL	FETAL	MATERNAL	FETAL
Local infection	6	0	2 (1 twin)	0	28.5	100	71.5
Gas sepsis	7	4	5	66⅔	71.5	33⅓	17⅔
Physometra Or, Emphysema	4	4	3	100	75	100	50

CONCLUSIONS

1. There is no specific cure for all cases.
2. Prompt massive doses of a polyvalent serum for streptococci and *B. welchii* upon admission, if present in the smears.

3. Repeated intrauterine cultures, douches, and transfusions, as soon as the organism has been identified by smears and cultures.

4. It is important to differentiate in all cases of fever, jaundice, cyanosis, and endometritis.

5. Combat acidosis, anemia, and low urinary output.

6. Debridement of necrotic areas over the body and the application of an oxygen-liberating solution as a wet dressing.

7. Prophylactic doses in those cases with positive smears, only.

8. Early extirpation upon recognition of uterine emphysema, as may be proved by a skiagram.

9. Gas producing bacteria should be of extreme importance to doctors in contact with rural patients because these are often found in the intestinal tract of herbivorous animals.

10. Its prevalence has been proved; it is not confined to warm climates; and the cause of death may be attributed to an unknown etiology.

11. Escaping gas from the genital tract is indicative of a severe infection and a fatal termination of the case usually occurs.

12. All instruments and materials should be fractionally sterilized before being used again because of the spore-bearing properties of the organism.

13. Strict isolation precautions are of great importance.

REFERENCES

(1) *Toombs, P. W., and Michaelson, I. D.:* Am. J. Obst. & Gynec. **15:** 379, 1928. (2) *Wrigley, A. J.:* Proc. Roy. Soc. Med. **23:** 1635, 1930. (3) *Falls, F. H.:* Am. J. Obst. & Gynec. **25:** 280, 1933. (4) *Bysshe, S. M.:* Ibid. **25:** 995, 1938. (5) *Toombs, P. W.:* Ibid. **14:** 415, 1932. (6) *Welch, Wm. H.:* Bull. Johns Hopkins Hosp. **11:** 185, 1900. (7) *Hill, A. M.:* J. Obst. & Gynaec. Brit. Emp. **43:** 201, 1936. (8) *Lash, A. F.:* Am. J. Obst. & Gynec. **15:** 288, 1933. (9) *King, J. Cash, and Russell, P. B., Jr.:* Radiog. & Clin. Photo. **10:** 5, 15, 1934. (10) *Brutt, H., and Lehmann, W.:* Klin. Wchnschr. **6:** 1510, 1927. (11) *de-Sa, H.:* Bull. Soc. d'obst. et Gynec. **25:** 639, 1936. (12) *Brown, T. K.:* Am. J. Obst. & Gynec. **20:** 300, 1930. (13) *Porter, Arthur R., Jr.:* J. Tennessee M. A. **21:** 9, 1929.

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DISCUSSION

DR. LEONARD A. LANG, Minneapolis, Minn.—A case of *B. welchii* infection came to our attention during the past year. The patient, a twenty-seven-year-old primigravida, had been admitted to the hospital for induction of labor by rupturing the membranes, the indication being post maturity. She failed to go into efficient labor, however, and at the end of the fourth day the patient was found to be fairly exhausted, with a pulse of 100, a temperature of 100° F., the cervix 3 cm. dilated, fairly thick and edematous. The fetal head was well above the spines, well flexed, and there was no evidence of cephalopelvic disproportion. The cervix reached full dilatation forty-eight hours later. By this time the temperature had gradually risen to 102° F., and pulse remained at a level of 120. The fetal heart tones had disappeared some twelve hours before full cervical dilatation was accomplished. During this latter period the uterus had increased in size to a well-rounded, very tender organ in which it was difficult to distinguish the relaxation between pains, and a fairly abundant foul discharge had developed.

A craniotomy was performed when the cervix reached full dilatation. During delivery, large amounts of gas under pressure and foul discharge emanated from the birth canal. The fetus was autopsied, and heart, lungs, and liver especially

showed gross evidence of gas bacillus invasion. Cultures from various organs produced heavy growths of *B. welchii* and hemolytic streptococci.

Following delivery the patient was given a single prophylactic dose of polyvalent serum. Sulfanilamide was given in large doses for the first few days, and two transfusions were given during the first week post partum. The temperature reached high points of 101° to 102° F. during the first five days, then dropped to normal and remained there until her discharge on the fifteenth post-partum day.

DR. R. J. CROSSEN, ST. LOUIS, MO.—At the St. Louis Maternity Hospital we have been using for years 1 per cent neutral acriflavine in glycerin, and it has cut down the incidence of infection very materially. We had a patient recently who went twelve days with ruptured membranes and no temperature elevation. I feel that the afebrile course and absence of infection were in a large part due to the use of daily vaginal instillations of acriflavine in glycerin during this period.

DR. RUSSELL (closing).—Many cases of *B. welchii* infection are probably not diagnosed because the attending physician fails to request smears from the cervix and vagina, as well as anaerobic cultures. This belief is substantiated by the fact that the senior author diagnosed, during one year, the greater number of cases appearing in the series by the above means. The economic importance of this organism cannot be underestimated as is shown by the history of the young child mentioned in this paper.

PREVENTION OF TUBERCULOSIS BEGINS BEFORE BIRTH*

TUBERCULIN TESTING DURING PREGNANCY AS A FERTILE FIELD FOR CASE FINDING AND PREVENTION

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UDO WILE[1] stated that early diagnosis of syphilis in pregnant women is good economics, as it makes possible the treatment of two patients for the cost of one. Eisele and Mason[2] found the incidence of unsuspected tuberculosis in the routine prenatal clinic to be 1.06 per cent as compared to 0.87 per cent of syphilis in the same group. These figures point toward the fact that it is even more important to diagnose early tuberculosis in pregnant women than to diagnose early syphilis. Furthermore, Kuss, Comby, Hamburger and Binswanger have reported that "From slightly more than 1 per cent to 6 per cent of all deaths in children from birth to three months are due to tuberculosis. From the third to sixth month some authors have reported as high as 27 per cent of deaths have been due to this disease. Indeed more deaths from tuberculosis occur in the first year than in any one year of the three score and ten."[3] Therefore, tuberculosis case finding, to be most economical and effective, should begin in the prenatal group. In this way maternal diagnosis is made before the birth of the child and infection of a new generation is prevented.

Since July, 1936, the obstetric history sheet of the Santa Clara County Hospital has had a space for the tuberculin test report and since that

*Presented in part by C. L. Ianne at the National Tuberculosis Association in symposium discussion of paper on "Mass Tuberculin Testing and X-raying."

time, this test has been done routinely on each patient visiting the prenatal clinic. On those entering the hospital during labor, who have not attended the prenatal clinic, the test is done immediately after parturition. Those reacting are given a chest x-ray and if found to have pathologic shadows, are referred to the sanatorium for advice and care. While in the Obstetrical Division, these patients are isolated to prevent infection of the patient and hospital personnel.

A series of maternal and infant deaths from tuberculosis in 1934 and 1935 and the fact that several young mothers were found to have far advanced tuberculosis post partum, prompted us to perform tuberculin tests on the prenatal group. Two other factors helped to make our

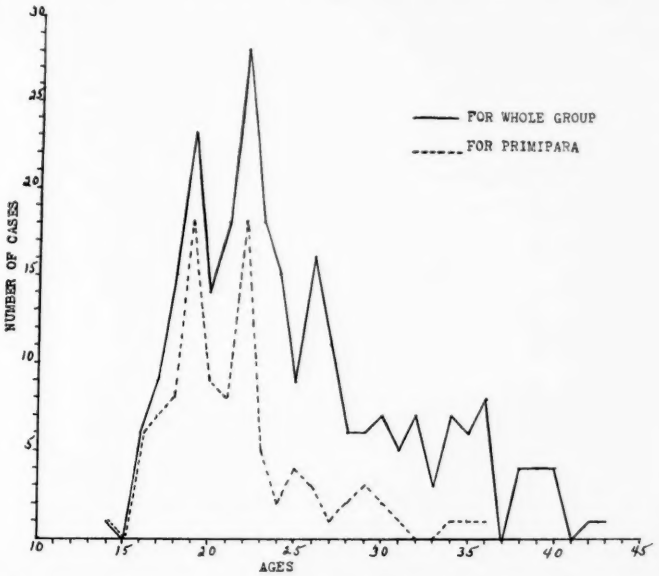

Fig. 1.—Graph showing age distributions of the 252 tuberculin reacting women and of the 97 primiparas who are included in the group.

obstetric service tuberculosis conscious: (1) the sanatorium division is adjacent to the general hospital and the interns and residents rotate part time through this service under supervision of the tuberculosis resident staff; (2) a member of the obstetric consulting staff had one year residency in the tuberculosis division.

The above cases were presented to the hospital staff meeting with the suggestion that all prenatals be tuberculin tested and the reactors x-rayed. This was finally approved but not without the usual fallacious comment: "Why tuberculin test when all adults are infected?"

Following the report of Korns[4] in the Cattaragus County, N. Y., Milbank Survey that only about 50 per cent of adults in rural communities reacted to the tuberculin test, we began to test all adults attending the chest clinic and found many nonreactors. Testing prenatal women gives us a group tuberculin survey of supposedly normal young adults who are not tuberculosis suspects. It also gives a good idea of the number

infected and the morbidity in the particular age and sex group in which the highest percentage of deaths occurs (Fig. 1).

The following cases will illustrate the damage done by unknown tuberculosis in the pregnant woman.

CASE 1.—A young married Mexican girl, aged 17 years, because of contact with one brother who died of tuberculosis and to a younger brother with generalized pulmonary tuberculosis, was examined in December, 1932 (aged 14), and again in December, 1933. Tuberculin test and x-ray of chest were negative. On June 20, 1935 the patient entered the hospital in labor, although otherwise apparently well. Physical examination of chest was negative. No x-rays of chest were taken. The child was born four days later and patient discharged after the usual time apparently well. Nine months later she attended the general medical clinic complaining of cough. A prescription was given for this and an x-ray taken with advice to return the following week. The cough subsided and the patient failed to return. She was seen by the tuberculosis clinic nurse a few months later during a visit to her brother

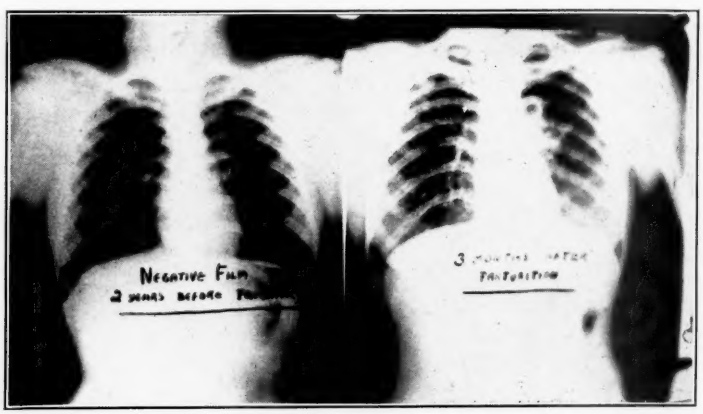

Fig. 2.—AL. Film Dec. 4, 1932: Chest clear. Film June 8, 1936: Shows mottling right upper half and infiltration left perihilar region.

in the sanatorium. Her general condition was noted and examination made. The film taken at this time showed progression of disease when compared with film taken on her first post-partum visit. Sputum was positive and patient admitted to the sanatorium June 16, 1936. Although apparently improving slightly at first, patient died in two years despite left phrenic paralysis, pneumothorax and pneumoperitoneum (see Fig. 2). She had nursed her child for ten months and, although chubby and apparently well, it was found to have bilateral bronchopneumonic pulmonary tuberculosis and died in the sanatorium, aged 18 months.

CASE 2.—A young American white woman, aged 20, contact with mother and a sister, both of whom died of tuberculosis, and whose younger sister later developed this disease, had a pregnancy with miscarriage, December, 1934. She became pregnant again and attended the prenatal clinic. No comments were found in case history indicating chest disease. Patient worked up to the date of delivery. She remained in bed one week after discharge and, suspecting her condition, weaned the child and went to see a private physician who referred her to the general clinic with a history that two days after the child was born, she began to cough and had about 5 c.c. of sputum. Night sweats, marked fatigue, and hemoptysis followed. On x-ray examination February, 1936, patient was found to have an advanced upper right lobe tuberculosis. She was referred to the chest clinic two weeks later and stated that previous to and during pregnancy she had "felt fine." No cough, fatigue, or

other symptoms, except a loss of weight, were noted during pregnancy. Sanatorium care was advised for collapse therapy. She refused, feeling that she could take care of herself at home on bed rest, as had been advised several years before for a sister. Becoming worse on this regimen, she was admitted three months later with progressive disease and bilateral cavitation. At present she is barely holding her own with an ineffectual pyopneumothorax right and a fairly good collapse left.

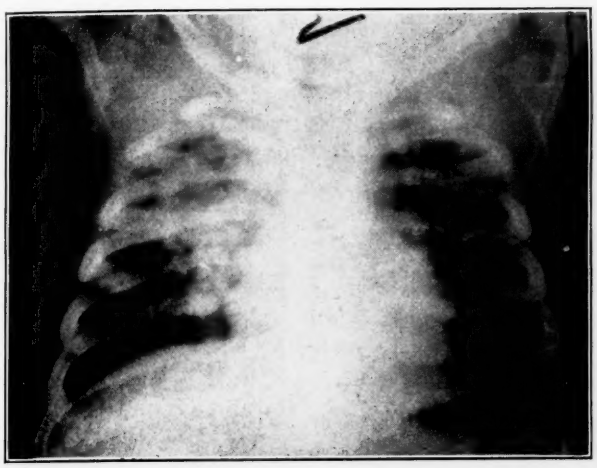

Fig. 3.—Baby L. Film Oct. 17, 1937 at age of twelve months shows bilateral generalized mottling. Child died aged 18 months.

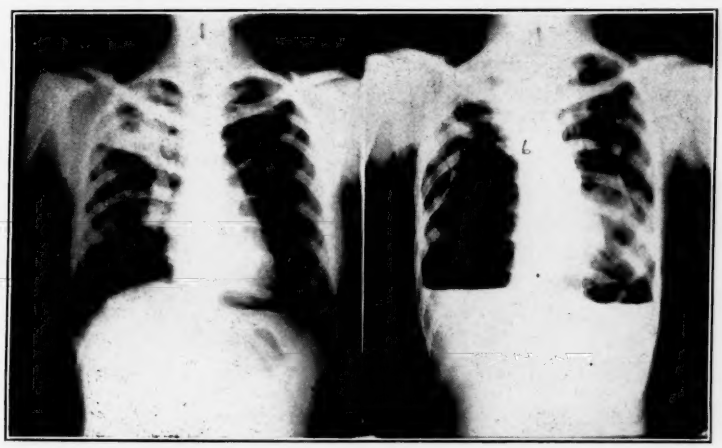

Fig. 4. Fig. 5.

Fig. 4.—RB. Film February, 1936: Shows heavy infiltration right upper with cavitation under clavicle.

Fig. 5.—Film Aug. 11, 1938: Shows bilateral partial artificial pneumothorax with numerous adhesions holding cavity open and fluid level above diaphragm. Left, artificial pneumothorax with heavy infiltration at base.

The child was taken to a nursery at ten weeks of age but not before infection had occurred as proved by positive tuberculin test. X-rays of the child's chest are apparently negative. Perhaps the fact that the child was weaned at ten days, when the mother recognized her condition, prevented repeated, massive infection, as occurred in Case 1.

At the end of the first six months of our survey, the figures were so impressive that a search of the literature was made, with the help of Dr. Kendall Emerson of the National Tuberculosis Association. This revealed that tuberculin testing has not been followed routinely in obstetric clinics. According to the Bureau of Maternal Welfare in Washington, nothing bearing on this work is on file in the United States Library. Vaughn[5] of Detroit states: "The tuberculin testing of prenatals is not a routine practice in our clinic. We are paying attention to individuals intimately exposed and those who live in areas of high mortality."

Through recent personal communication we find that Dr. Charles Cawood,[8] Health Officer of Fayette County, Kentucky, has also been tuberculin testing all patients attending the prenatal clinic since 1936.

Nicklas[6] mentions the use of the x-ray in finding early unsymptomatic tuberculosis in the expectant mother.

Although Block[7] of the University of Chicago considers the x-ray ideal for group examination, he feels that the expense makes it impractical and only x-rays those who have suspicious findings on fluoroscopic examination. He states the objections to this method of screening are the necessity for trained examiners and the element of time. In addition to the above, our objection is that the fluoroscope gives us no permanent record, and it does not reveal the total number of infected cases. Tuberculin testing tells us this and permits following of the family group. Block does not use the tuberculin test in group examination because of the large percentage who would fail to return for readings. We have overcome this difficulty by having the Public Health Nurse call and read the tests for those who fail to return. Block states that an additional objection to the tuberculin test as a method of screening out tuberculosis in adults is the high incidence of infection. He feels that it would be more economical to use the fluoroscope and x-ray only, whereas the test might be used successfully for children where the percentage of infection is much lower. This is not the case in our community where the percentage of infection in adults is 41 per cent, which is only a small percentage higher than in the high school group of a few years ago. We find that screening out negative reactors results in a definite saving of films and the time and work incidental to this procedure.

Other than the above references to early diagnosis, a review of the literature on tuberculosis and pregnancy disclosed mainly a discussion of the mortality and morbidity of tuberculosis during pregnancy. Most of this is very controversial and, except for personal impression and discussion as to whether pregnancy is harmful and whether it should be allowed to proceed or not, little is found.

Ornstein and others,[9] from a statistical study of a large group with tuberculosis, feel that pregnancy has little or no effect on the productive type of tuberculosis, whereas it is fatal to the exudative type. Skillen and Bogen,[10] in a study of 10,000 admissions to Olive View Sanatorium, Olive View, California, find that pregnancy in tuberculous women did not alter the fate of tuberculosis in comparison to a similar

nonpregnant group of women with tuberculosis, but that "The occurrence of pregnancy should not allow neglect of the pulmonary condition before, during and after obstetric management."

Before we began to discover early tuberculosis by tuberculin tests and before the general use of collapse therapy, it was our opinion that tuberculosis was definitely incited or made worse by pregnancy. Since the beginning of this survey we rarely find far-advanced tuberculosis in a post-partum patient.

Only three patients with far-advanced tuberculosis have been seen. One of them did not attend the prenatal clinic but was admitted in labor. This was during the early months of our survey and she was not tuberculin tested. One did not react to the first dilution of the test and delivered before the second dilution could be given. She was not x-rayed. This patient was admitted to the hospital twelve months post partum with hemoptysis and bilateral cavitation. The third had a positive tuberculin test but, due to clerical omission, this was not recorded on her chart and therefore no x-ray was taken. She was recently admitted to the sanatorium with far-advanced caseocavernous tuberculosis.

This brings us to the conclusion that tuberculosis and pregnancy are not incompatible *if tuberculosis is diagnosed early and collapse therapy can be instituted.*

STATISTICAL STUDY

A total of 805 women were tuberculin tested; 114 women, or 14 per cent, failed to return for a reading. Of the 691 women who were tuberculin tested and read, 407, or 58.9 per cent, were negative and 284, or 41.1 per cent, were positive to a 1:1,000 dilution of old tuberculin. Of the 284 tuberculin reactors 252 were x-rayed. Thirty-two tuberculin reactors failed to return for x-rays. This may be attributed to the fear of some newlyweds to let their husbands know that they may have tuberculosis, as was suggested by Block in his Chicago survey.

Table I reveals the number of tuberculin reacting patients for each gravida and the mean age for each group. It is to be noted that 177 women, or 70 per cent, of the total 252 tuberculin reacting women x-rayed, were having their first, second, or third pregnancy. The average age of these 177 women comes well within the age group commonly reported as having the highest incidence of tuberculosis deaths (see Table I).

TABLE I. TWO HUNDRED FIFTY-TWO TUBERCULIN REACTING PREGNANT WOMEN

GRAVIDA	NO. PRENATALS	MEAN AGE
i	97	21
ii	47	23
iii	33	22
iv	18	26
v	14	24
vi	10	31
vii	6	33
viii	6	32
ix	3	31
x	5	32
xi	8	36
xii	2	33
xiii	2	35
xiv	1	40

TABLE II. PATIENTS WITH DEFINITE PULMONARY LESION FOUND AMONG POSITIVE REACTING PRENATALS

PT.	CASE	AGE	GRAV.	LESION	SPUTUM	DATE ADMISSION TO SANATORIUM	DATE OF DELIVERY	TREATMENT INSTITUTED	DISCHARGE AND CONDITION	TUBERCULIN TESTING OF CHILDREN			
										NEWBORN		OTHER, LIVE	
										POS.	NEG.	POS.	NEG.
DB	2481	22	i	*RL* cavity with questionable infiltration. Second anterior I.S. upward. *LL* negative minimal tuberculosis	None	2/27/37	5/17/37	Sanatorium care with Pnx. right Mar. 9, 1937. Baby cesarean section. Right Pnl. Jan. 19, 1938	Discharged July 29, 1937. Satisfactory Pnx. Syphilis under treatment	0	1	0	0
TC	2750	21	ii	*RL* soft infiltration 5th R.P. *LL* mottled density second anterior I.S. to apex. Moderately advanced tuberculosis	None	6/17/38	6/10/38	Sanatorium care with phrenic crush, left. Pnx. failure July 11 and 19, 1938	Still in sanatorium	D at 2 mo.		0	1
MD	2473	27	iv	Far advanced bilateral tuberculosis cavity	None	3/ 3/37	2/ 9/37	Sanatorium care. Premature rupture of membranes. Dilatation and curettage. No Pnx. Patient left	Patient signed a release Mar. 28, 1937	Not tested		0	1
LG	252	34	xiii	*RL* minimal apical tuberculosis	None	3/14/37	6/ 1/37	Sanatorium care with Pnx. right attempted. No space. Right phrenic crush Apr. 8, 1938. Pregnancy term. Feb. 15, 1938 at 4 mo.	Discharged Apr. 22, 1938. Satisfactory. At home	0	1	1†	9

Pnx, pneumothorax; Pnl, pneumonolysis; D, died; Stom, stomach; RL, right lobe; LL, left lobe; IS, interspace; RP, rib posterior.
†Child by first husband who had active far advanced tuberculosis.

MG	2555	31	vi	*RL* mottled density apex to fifth P.R. honeycombing. *LL* negative. Minimal tuberculosis right, fibroid	None	6/21/37	6/11/37	Sanatorium care. Pnx. right June 7, 1937	Discharged July 22, 1937. Pnx. discontinued by patient. Uneducated. Not being followed up	0	1	2	3
IK	2581	34	vi	Minimal apical tuberculosis fibroid arrested	None	Not admitted	6/ 5/37	Rest regime post partum at home	Satisfactory. Referred to sanatorium clinic for follow-up	0	1	1	1
LL	2723	17	i	*RL* mottling with calcification upper. *LL* soft infiltration second I.S. May 12, 1938 anti-partum moderately advanced tuberculosis	None	6/22/38	6/12/38	Sanatorium care. June 30, 1938 post partum. Cavity 3½ × 3 cm. left. Pnx. left July 25, 1938	Still in sanatorium. Pnx. Satisfactory collapse	0	1	0	0
LR	2371	18	ii	*RL* soft floc. 1st. I.S. *LL* thumb print sixth I.S. Minimal tuberculosis	None	9/16/36	8/24/38 and 5/27/38	Sanatorium care. Pnx. Sept. 27, 1936. Baby cesarean section	Discharged Mar. 15, 1937. 2nd. pregnancy May 27, 1938 normal delivery	First D at 3 mo. 2nd not tested		0	0
RR	2826	33	ii	Minimal arrested tuberculosis. ??? Child positive tuberculin test.	None	Not admitted	4/27/37	Home rest	Satisfactory	1	0	0	1
JR	2599	26	vi	*RL* soft mottling first *LL* second anterior I.S. to apex soft mottling. Moderately advanced tuberculosis	Negative	7/16/37 and 8/24/38	6/23/37	Pnx. bilateral. Right Oct. 18, 1937. Left Sept. 13. 1937. Pnl. bilateral because of adhesions	Still in Sanatorium	D at 3 mo.		5	0
AT	2374	19	ii	Suspicious tuberculosis May 20, 1933. Definite progressive with pregnancy. Minimal tuberculosis left	Neg. Stom. lavage pos.	4/ 1/38	11/10/36	Sanatorium care with Pnx. left. May 9, 1938	Pnx. O.K.	0	1	0	1
GV	2531	27	v	Minimal arrested tuberculosis right	None	Not admitted	12/16/37	Rest program at home	X-ray post partum O.K.	Not tested		0	2

X-RAY FINDINGS

Of those x-rayed, 203 were found to have negative films; 37 had calcifications in the hilum or lung fields. Most of the latter were x-rayed or fluoroscoped three months after birth of child and none found to have activated. Twelve, or 1.7 per cent, had adult or reinfection type of lesion, mainly apical. Of these, 10 were minimal, 1 moderately advanced, and 1 far advanced. None had positive sputum. One was an observation case with infiltration of the left base, etiology undetermined. Upon pregnancy there was an extension of infiltration with positive stomach lavage and a diagnosis of minimal tuberculosis was established. The one with moderately advanced lesion was known to the chest clinic as an apparently arrested case; reactivation was suspected on pregnancy. The far-advanced case was definitely asymptomatic and not known to the clinic. In 5, diagnosis was established before the third month of pregnancy and 5 others one month or less before term. Two patients were found after delivery.

TREATMENT

Sanatorium care was recommended for nine of these. Two (DB, MG) had pneumothorax established before term; 5 (LL, M.G., AT, JR, LR) as soon as they had convalesced from childbirth; 2 had temporary phrenic paralysis because of failure to induce pneumothorax. Only one of the above (LG) had hysterotomy with ligation of tubes. This was her thirteenth pregnancy and she had an active lesion. MD, with advanced tuberculosis, signed a release and left the sanatorium before pneumothorax was established. No follow-up was possible as patient had left the county. Two (IK, GV) had apparently arrested minimal lesions and modified bed rest was advised. One (RR) had no recommendation due to oversight (see Table II).

FATE OF THE NEWBORN

A survey of the babies shows that 13 were born alive. One (LR) mother had a second pregnancy during the period of this survey. Eleven of the babies are still living. One died of injuries at four months; two of diarrhea at one and two months. Of the 11 living babies, 9 have been tuberculin tested, one reacting. The mother of this child had a minimal lesion which was overlooked but found on review of films after child was born. We have so far attempted to tuberculin test only the babies and other members of families where a reinfection type of lesion has been found.

BENEFITS DERIVED

As mentioned above, we believe that prevention or postponement of actual disease by institutional care of the mother and initiation of collapse therapy before or soon after delivery is of great benefit. The family is spared a mother who would otherwise be an invalid. The newborn, the family, and the community are protected from the infection that occurs before symptomatic tuberculosis becomes manifest. Hospital patients are screened against a communicable disease and protection is afforded the hospital and patient personnel. Nursing the infant is prohibited and the massive infection that usually results in early infant death is prevented. The additional strain of caring for the child is obviated and the mother's general health is maintained. This period is considered by many to be the "last straw" in the causation of disease.

If the follow-up work is properly carried out, the remainder of the household is tuberculin tested and reactors x-rayed. *This is not done where the fluoroscope or x-ray is used as a screen.* Through this family follow-up, the husband of one of our prenatals, not in this group, was found to have a moderately advanced lesion with positive sputum and was removed to the sanatorium. In this case, infection of the newborn infant was definitely prevented.

SUMMARY

After some seemingly unnecessary tuberculosis deaths following pregnancy, tuberculin tests, with x-rays of the reactors, were added to our routine procedure for the examination of prenatals.

Between June 1, 1936, and June 1, 1938, 805 women in the so-called "dangerous" age were tested. Six hundred ninety-one tests were read. Two hundred eighty-four, or 41+ per cent, reacted and 407, or 58.9 per cent, did not react to old tuberculin 1:1000. Of the reactors 252 were x-rayed; 32 failed to return. The x-rays revealed 10 cases of minimal tuberculosis, one moderately advanced, and one far advanced. Nine were admitted to the sanatorium before or immediately after delivery and pneumothorax established in seven. Two had phrenic paralysis when pleural space was not found. Three with inactive lesions were treated at home.

None of the reactors, including those with lesions, have had extension or clinical manifestation of disease. Most of the mothers with satisfactorily established pneumothoraces are home caring for their families. Only one of the children has been infected to date. It is gratifying to note that there have been only two deaths in the first year of life since 1934 in Santa Clara County, a mixed urban and rural community of 160,000. These occurred in 1935. In 1937 there was only one death in the age group from one to ten years.

CONCLUSIONS

1. The routine use of the tuberculin test in prenatal care is a method that can be easily used in clinics and private practice for discovery of active tuberculosis.

2. Forty-one per cent of patients who returned for reading had positive tuberculin tests.

3. Unsuspected, active tuberculosis occurred in 1.7 of those read.

4. The cost of fluoroscopy or x-ray for the tuberculin reactors would be very little more than the cost of routine Wassermann.

5. Early diagnosis permits early institution of collapse therapy, thus permitting pregnancy to continue without extension of pulmonary disease.

6. Although this is a small group and the time elapsed short, the findings are of sufficient public health value to recommend it as a routine preventive measure. Prevention of tuberculosis should begin before birth.

REFERENCES

(1) *Wile, Udo:* Univ. of Mich., talk before San Jose Hosp. Staff, June 1, 1938. (2) *Eisele and Mason:* Am. J. Obst. & Gynec. **36:** 387, 1938. (3) *Kuss, Comby, Hamburger, and Binswanger:* Modern Aspects of Diagnosis, Classification of Tuberculosis (Sept., 1927), Chap. 5, p. 44. (4) *Korns, John H.:* Am. Rev. Tuberc. **28:** 260, 1933. (5) *Vaughn, Henry H.:* Health Commissioner, Detroit—Personal communication. (6) *Nicklas, J.:* The Tuberculous Child—talk at annual meeting American Academy of Tuberculosis Physicians, San Francisco, June, 1938. (7) *Block, R. G., et al.:* Am. Rev. Tuberc. **37:** 174, 1938. (8) *Cawood, Charles:* Health Officer, Fayette Co., Ky., Personal communication. (9) *Ornstein, et al.:* Am. Rev. Tuberc. **31:** 224, 1935. (10) *Skillen and Bogen:* J. A. M. A. **111:** 1153, 1938. (11) California Tuberculosis Assoc., News Letter, May, 1938.

TREATMENT OF THE MENOPAUSE WITH ESTRADIOL DIPROPIONATE*

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AN ESTROGENIC substance is any substance which has activities similar to those exhibited by the hormone of the ovarian follicle. In the human being, 3 chemically distinct and biologically active estrogenic substances have thus far been isolated. Estradiol has been separated from follicular fluid in crystalline form and presumably is the true follicular hormone.[1] Estrone (theelin) and estriol (theelol) are found in pregnancy urine,[2] placenta[3] and presumably in nonpregnant urine. They probably represent excretion forms of the metabolized estradiol.[4-6] Various observers do not agree as to the exact potency of these 3 compounds, but do agree that estradiol is more potent than estrone and that estriol is the least potent of the 3 substances.

It has been demonstrated by various workers that esterification of estradiol or estrone leads to a more prolonged physiologic effect on parenteral administration. This enhanced effect is due, presumably, to slower absorption of the compound.

In 1937 Miescher and Scholz[7] synthesized estradiol dipropionate, which is the doubly esterified form of estradiol. In this compound the 2 hydroxyl groups on the molecule have been replaced by propionic acid radicles. Miescher, Tschopp and Scholz[8] have investigated the relative potency of this substance, with other esterified forms and with free estrone and estradiol. According to these workers the minimal effective dose or rat unit of estrone, estradiol benzoate, and estradiol dipropionate is the same, 0.00075 mg. Other workers agree fairly well on this rat unit for estrone but believe the rat unit for estradiol benzoate to be lower. Miescher and his coworkers found a marked difference in physiologic effect between these compounds. If 0.05 mg. of estrone, estradiol benzoate, or estradiol dipropionate were injected into castrate rats, the animals would go into estrus. In the estrone injected animals this estrus would persist for four or five days. In the animals injected with estradiol benzoate, estrus would persist for fourteen days. In animals injected with estradiol dipropionate, estrus would persist for forty-two days. Similar differences were noted when growth of the rat uterus was used as the criterion of estrogenic effectiveness. With the same dosage (0.05 mg.) the effect of estrone persisted eight days, with estradiol benzoate twenty-four days, and with estradiol dipropionate, sixty days.

The value of estrogenic substances in the treatment of menopausal symptoms is quite well established. However there is little agreement of opinion as to which substance should be used, or the method or frequency of administration. We are well aware of the fact that desiccated thyroid or sedatives may be of value in some menopausal patients. Some individuals may even be improved by suggestion therapy. However, it

*Presented at a meeting of the Chicago Gynecological Society, March 17, 1939.

is very doubtful whether true menopausal symptoms such as the hot flush can be relieved in all patients by such means. Estrogens, if given in adequate dosage, will relieve these symptoms in all patients. The one qualification that must be added to this statement is that the symptoms the estrogens are expected to relieve must truly be menopausal symptoms and not entirely independent or even unrelated symptoms present in the woman of menopausal age.

Estrogens are effective by a variety of routes: the oral, the percutaneous or the parenteral. With the exception of estriol glucuronide (emmenin)[9] which is of low potency, natural estrogens are many times more effective by parenteral administration than when given orally. Estrogens are at the present time quite costly. Their price per effective mouth unit is such that treatment of the ordinary patient with dosages adequate to control menopausal symptoms is financially prohibitive.

Several workers have shown that estrogens are absorbed through the skin and have systemic effects after percutaneous administration.[10-13] According to Zondek[10] estrone in solution in alcohol, benzene, or ether is as effective percutaneously in the experimental animal as it is subcutaneously in oil. In oil or ointment solution it is only one-seventh as potent percutaneously as it is subcutaneously. Whether this relative effectiveness by percutaneous administration is equally as true in the human being has yet to be shown. A report by Salmon[13] and experiments in progress by one of us (R. R. G.) would indicate that this is doubtful.

At the present time the majority of patients are given estrogenic therapy by the intramuscular route. In this country, at least, injections are usually given 2 to 4 times weekly. Intramuscular injections are not pleasurable. Any estrogenic substance, then, that would control menopausal symptoms and that which could be given with a minimal frequency would be desirable.

In view of the enhanced potency and prolonged physiologic effect of estradiol dipropionate in the experimental animal, it was thought worth while to determine the clinical value of this substance in the treatment of menopausal symptoms in the human female.

METHODS AND RESULTS

Sixty-two menopausal patients have been treated with estradiol dipropionate.* Only 55 of these patients will be considered in this report. The remaining 7 patients are not included either because they had been observed over too short a period of time (under three months) or because their clinic attendance was so poor that it was not possible to estimate their maintenance dosage.

The symptoms of the menopausal patient are many and varied. However, such patients have one common symptom, the hot flush. In view of this fact, the patients were instructed to keep an accurate record of the frequency and severity of the hot flushes. These data were used to a large extent as the index of the success of therapy. It was noted that with disappearance or return of the hot flushes there was a corresponding subsidence or exacerbation of such symptoms as nervousness, irritability, fatigue, headaches, etc.

*Estradiol dipropionate under the trade name "Di-ovocyclin" has been furnished through the courtesy of Dr. Ernst Oppenheimer of Ciba Pharmaceutical Products Incorporated.

The dispensary patients were seen once a week, the few private patients occasionally at more frequent intervals. It was found that patients were rendered symptom-free more rapidly by giving large doses (2.0 to 5.0 mg.) for the first few treatments. No patient was treated more often than once a week. After a patient was free from the hot flushes (usually one to three weeks) an attempt was made to determine her maintenance dosage. This was a rather difficult procedure, being largely a matter of trial and error. However, by gradually lowering the dose, and prolonging the interval between treatments, at least the approximate maintenance dosage was determined which would keep each patient either entirely symptom-free or having not more than 1 or 2 hot flushes during the course of a week.

A slight diminution in necessary dosage was observed in only a few patients during the experimental period. This is probably due to the fact that only a relatively short period of treatment is considered in this study. Patients included in this series are limited to those treated from three to nine months only.

Slight and temporary reappearance of symptoms was noted in a few patients, associated with upper respiratory infections, or periods of unusual emotional stress.

The ages of the patients in this series varied from 29 to 59 years, with an average age of forty-three years. Twenty-nine were "normal" menopausal patients, 23 postoperative and 3 postradiation. The average age of the patients and the average duration of the symptoms are shown in Table I. There was no definite correlation between the necessary maintenance dosage and either of these factors. The total dosage per month per patient has also been calculated but no definite correlation was found with the age or length of symptoms.

In theory, at least, one would expect that the necessary maintenance dosage would be less in patients whose symptoms had been present a long time in contrast to those in whom the symptoms were of recent origin. In a larger series of patients such a correlation might be present.

TABLE I. DETAILS OF TREATMENT

DOSE IN MG.	INTERVAL IN WEEKS	NUMBER OF PATIENTS	AVERAGE LENGTH OF SYMPTOMS MONTHS	AVERAGE AGE YEARS
0.2	2	1	6.0	36.0
0.5	1	3	6.0	49.7
1.0	1	6	7.8	41.0
1.0	2	14	12.3	42.3
1.0	3	2	6.5	42.5
1.0	4	1	12.0	48.0
2.0	1	6	37.0	45.0
2.0	2	3	14.25	37.3
5.0	1.0	6	10.0	42.0
5.0	1.71	3	19.5	43.6
5.0	2.0	7	38.0	43.0
5.0	3.0	2	30.0	40.5
5.0	4.0	1	12.0	59.0

TABLE II. NECESSARY FREQUENCY OF TREATMENT

	TREATED ONCE A WEEK	TREATED EVERY 10 DAYS	TREATED EVERY 2 WEEKS	TREATED EVERY 3-4 WEEKS	TOTALS
Number of patients	21	3	25	6	55
Per cent of patients	38.18	5.45	45.45	10.92	100

	TREATED EVERY 7 TO 10 DAYS	TREATED EVERY 2 TO 4 WEEKS	TOTALS
Number of patients	24	31	55
Per cent of patients	43.64	56.36	100

The necessary frequency of treatment is shown in Table II. Twenty-one of the 55 patients had to be treated once a week for maintenance therapy, 3 every ten days, 25 every second week, and the remaining 6 every third or fourth week. A further analysis of these data shows that 43.64 per cent of the patients could be maintained with treatment once every seven or ten days and 56.36 per cent of the patients by treatment once every second to fourth week.

These data indicate that estradiol dipropionate is clinically valuable in that treatment may be given at relatively infrequent intervals. The individual dosages may seem quite high but the dosage when considered on a monthly basis is not very large in the majority of patients (Table III). The maintenance dosage per four weeks in the 55 patients was 2.0 mg. or less in 21, 4.0 to 5.0 mg. in 10, 7.5 to 10.0 mg. in 15 and 15.0 to 20.0 mg. in 9; 56.36 per cent of the patients received 5.0 mg. or less per month and 27.27 per cent received 7.5 to 10.0 mg. per month; 16.37 per cent received what may be considered a fairly high dosage of 15.0 to 20 mg. per month.

TABLE III. TOTAL DOSAGE PER 4 WEEKS

	2.0 MG. OR LESS	4.0 TO 5.0 MG.	7.5 TO 10.0 MG.	15.0 TO 20.0 MG.	TOTALS
Number of patients	21	10	15	9	55
Per cent of patients	38.18	18.18	27.27	16.37	100

	5.0 MG. OR LESS	7.5 TO 20.0 MG.	TOTALS
Number of patients	31	24	55
Per cent of patients	56.36	43.64	100

Patients were observed and questioned for systemic reactions but none were noted. Twelve patients had some recurrence or exaggeration of uterine bleeding. In 3 patients the bleeding was rather profuse but ceased when treatment was discontinued for a short interval or when the dosage was lowered.

A comparison of the clinical effectiveness of identical amounts of estradiol dipropionate and estrone has been made. Eleven patients of this series whose maintenance dosage of estradiol dipropionate had been determined, have been given the same amount in milligrams of estrone at the same time intervals. The patients were not informed of this substitution. Ten of the 11 patients had a recurrence of symptoms under treatment with estrone. When estradiol dipropionate was again given, the symptoms disappeared.

One patient of this group (Fig. 1) had a maintenance dosage of 2.0 mg. of estradiol dipropionate once a week. When estrone was substituted symptoms recurred in five days. Six patients had a maintenance dosage of 1.0 mg. of estradiol dipropionate once a week. When estrone was substituted symptoms recurred in 5 of 6 patients in one to two weeks (average 1.6 weeks). Findings in the sixth patient are considered inconclusive because of irregular attendance to the clinic. Three patients had a maintenance dosage of 1 mg. of estradiol dipropionate every two weeks. With estrone symptoms recurred after two to four weeks (average 2.66) of treatment. One patient had previously been treated with 0.2 mg. of estrone a week with some improvement but not complete cessation of hot flushes. Her maintenance dosage of estradiol dipropionate for complete relief of symptoms was found to be 0.2 mg. of estradiol dipropionate every two weeks. When estrone was substituted flushes recurred at the end of the third week. One week after the return to estradiol dipropionate, symptoms ceased.

Weekly vaginal smears have been examined on 6 of these menopausal patients. The smears have been interpreted according to the criteria of Papanicolaou (Fig. 1). He has shown that in the human being the menopausal smear is characterized by few or no squamous epithelial cells and with varying proportions of small round epithelial cells with large nuclei and leucocytes. Under adequate estrogenic therapy the vaginal smear consists almost exclusively of large flattened squamous epithelial cells with small darkly staining, pyknotic nuclei.

Two of these patients received 1.0 mg. once every two weeks and their smears were consistently of the menopausal type under treatment with both estradiol dipropionate and estrone. In the other 4 patients with dosages of 1.0 or 2.0 mg. of estradiol dipropionate per week the smears were of the estrus or follicular type. When estrone was substituted after a lag of one or two weeks the smears regressed toward the menopausal types containing varying proportions of squamous epithelial cells, small round epithelial cells and leucocytes. One to two weeks after estradiol dipropionate was resumed, the smears again returned to the estrus type.

In addition to these menopausal patients, vaginal smears were made weekly on 4 patients who had been treated and cured of a vaginitis with estradiol dipropionate. One patient with senile vaginitis had been found to maintain a consistent smear of squamous epithelial cells on 1.0 mg. of estradiol dipropionate once a week. When estrone was substituted, there was a gradual regression of the smear to the menopausal type. At the end of the third week of estrone the smear consisted of equal proportions of squamous epithelial cells, small round epithelial cells and leucocytes.

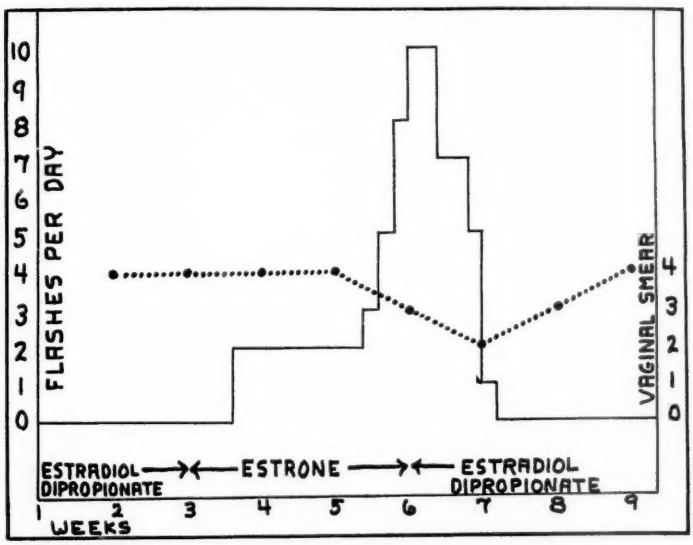

Fig. 1.—Solid line shows number of hot flushes per day. Dotted line shows state of vaginal smear. This patient had been standardized at 2 mg. of estradiol dipropionate for six months. *4*, Smear of squamous epithelial cells. *3*, Smear of squamous epithelial cells and small round epithelial cells. *2*, Smear of few squamous, many small round epithelial cells and a few leucocytes. *1*, Smear of small round epithelial cells and leucocytes in equal proportions. *0*, Smear of mostly leucocytes and a few small round epithelial cells.

Three other patients had been treated for infantile vaginitis. In these patients it had been found that an estrus smear could be maintained for two weeks with 1.0 mg. of estradiol dipropionate. When estrone was substituted and the smear examined one week later, in addition to squamous epithelial cells, a few small round epithelial cells and leucocytes were found in 2 of these patients. At the end of the second week the smears in both had regressed almost completely to the infantile type. In the third patient, it was found that estrone would maintain the estrus smear for one week, but at the end of the second week the smear was made up of small round cells and leucocytes.

On the basis, then, of recurrence of subjective symptoms in 10 of 11 menopausal patients and objective vaginal smear changes in 8 patients, estradiol dipropionate is clinically more effective per milligram in the human being than is estrone.

DISCUSSION

This clinical study must not be interpreted as presenting data as to the absolute minimal, total dosages of estradiol dipropionate necessary to

control symptoms in menopausal patients. The emphasis has rather been on an attempt to determine if this substance would be clinically valuable when given in moderate dosages at infrequent intervals. It is quite possible that some of the patients who received treatment of 1.0, 2.0, or 5.0 mg. at two- to four-week intervals could have been maintained with smaller, total monthly dosages if treated at more frequent intervals. At any rate, this particular substance has a prolonged effect in the human being similar to that observed in the rat.

This prolonged clinical effectiveness is qualitative. It is not due merely to the dosages used. This is indicated by the fact that estrone, a substance that is supposed to have the same minimal effective dose or rat unit has been subjectively and objectively inadequate when substituted for estradiol dipropionate.

We do not, however, wish to indicate that we consider this method the only way to treat patients with estrogenic substances or that estradiol dipropionate is the one and only ideal estrogenic hormone. It is possible that in the near future the natural estrogens (estrone, estradiol, estriol) will become sufficiently inexpensive for all such therapy to be given by mouth. This oral route would probably be preferred by many patients. It is also possible, though, that some would prefer an intramuscular injection once every one or four weeks rather than a pill by mouth 3 times each day.

Another possibility is that the use of the natural estrogens in the free or esterified forms will be completely supplanted by the new potent estrogens of a more simple chemical structure as discovered by Dodds and his co-workers.[15-17] One of these synthetics, di-ethyl stilboestrol, has been used for estrogenic therapy in human beings by several English workers.[18-23] These workers have reported, however, nausea with occasional vomiting and epigastric pain in 9 per cent to 67.7 per cent of treated patients. It remains to be seen whether this complication is merely due to the method of administration or is inherent in the compound.

SUMMARY AND CONCLUSIONS

Estradiol dipropionate has been shown by previous workers to have a very prolonged estrogenic effect in the experimental animal. Evidence is presented that this compound also has a prolonged effect in the human being It is of unusual clinical value in that injections may be given at infrequent intervals. A comparison with estrone has shown estradiol dipropionate to be clinically more effective.

REFERENCES

(1) *MacCorquodale, D. W., Thayer, S. A., and Doisy, E. A.:* J. Biol. Chem. **115:** 435, 1936. (2) *Doisy, E. A., Veler, C. D., and Thayer, S. A.:* Am. J. Physiol. **90:** 329, 1929. (3) *Collip, J. B.:* Proc. Calif. Acad. Med. **1:** 38, 1931. (4) *Pincus, G., and Zahl, P. A.:* J. Gen. Physiol. **20:** 879, 1937. (5) *Pincus, G.:* Symposia of Quantitative Biology **5:** 44, 1937. (6) *Westerfield, W. W., and Doisy, E. A.:* Ann. Int. Med. **11:** 267, 1937. (7) *Miescher, K., and Scholz, C.:* Helv. Chim. Acta **20:** 263, 1937. (8) *Miescher, K., Tschopp, E., and Scholz, C.:* Biochem. J. **32:** 725, 1938. (9) *Greene, R. R., and Ivy, A. C.:* Endocrinology **22:** 28, 1938. (10) *Zondek, B.:* Lancet **1:** 1107, 1938. (11) *Jadahson, Neplinger, and Zuercher:* Helv. Med. Acta **4:** 199, 1937. (12) *Loesser, A.:* J. Obst. & Gynaec. Brit. Emp. **44:** 701, 1937. (13) *Salmon, U. S.:* Proc. Soc. Exper. Biol. & Med. **38:** 439, 1938. (14) *Dodds, E.*

C., Fitzgerald, M. E. H., and Lawson, W.: Nature **140:** 722, 1937. (15) *Dodds, E. C., and Lawson, W.:* Ibid. **139:** 627, 1937. (16) *Idem:* Ibid. **139:** 1068, 1937. (17) *Dodds, E. C., Goldberg, L., Lawson, W., and Robinson, R.:* Ibid. **141:** 247, 1938. (18) *Bishop, R. M. F., Boycott, M., Zuckerman, S.:* Lancet **1:** 5, 1939. (19) *Wintertion, W. R., and MacGregor, T. N.:* Brit. M. J. **1:** 10, 1939. (20) *Loesser, A. A.:* Ibid. **1:** 113, 1939. (21) *Varangot, J.:* Lancet **1:** 296, 1939. (22) *Bishop, P. M. F.:* Ibid. **1:** 354, 1939. (23) *Wintertion, W. R.:* Ibid. **1:** 416, 1939.

DISCUSSION

DR. M. EDWARD DAVIS.—This report on the treatment of the menopause with estradiol dipropionate emphasizes the importance of choosing the proper available estrogenic substance. The prolonged and more pronounced effect of this estrogenic hormone which probably represents the true follicular substance simplifies therapy and provides more favorable results. Our work confirms all of the observations of the authors.

Some time ago we began the use of estrogens in suitable ointments for local application. This method of therapy should theoretically be ideal for it obviates the necessity of hypodermic administration and provides a constant hormonal effect. We have used this preparation in approximately 40 patients with menopausal symptoms and have found that it was of value in less than half of this group of women. In a number of our patients this type of medication provided only partial relief. From these preliminary observations, we have concluded that estrogens cannot be provided the patient as readily by the percutaneous route as by hypodermic administration.

Dodds, Lawson, and their co-workers have more recently introduced synthetic compounds with estrogenic activity. During the last year these compounds have been available for animal experimentation and clinical use. Most of these synthetic organic compounds are derived from a chemical compound designated as stilboestrol by Dodds and others. It has been found that these substances are several times more active than the natural estrogens, that they produce all of the changes that can be ascribed to the use of natural substances, and that they are as effective by oral administration as when administered parenterally. These substances provide us with a new type of medication, for oral administration is most desirable. These synthetic compounds will likewise reduce tremendously the cost of estrogenic medication. During the past four months we have treated a number of patients with these artificial estrogens and have secured excellent results. The only undesirable manifestations which we have noted have been occasional nausea, vomiting, and headache. Only additional observations will determine whether these manifestations occur too often to make the use of these preparations undesirable.

It is our impression that these new synthetic organic compounds will simplify the therapy of the menopause as well as the treatment of all other conditions where estrogens have been found effective.

DR. R. R. GREENE (closing).—By "natural estrogens," we meant the natural estrogens found only in the human being. There are several other estrogens found in animals, as for example in the pregnant mare.

We have had no experience with the stilboestrol referred to by Dr. Davis. The matter of nausea and vomiting with this particular substance is an observation not only on the part of Dr. Davis but also in the English literature, where there are 6 reports concerning patients who were given it by mouth. One man gave it by subcutaneous injection, and he also reported nausea and vomiting. The amount of nausea and vomiting varied from 9 per cent to 68 per cent of the patients in the different reports. Whether this nausea and vomiting is inherent in the stilboestrol or is due to too rapid absorption is not known. Recently it has been esterified and has been used in animals in the form of the dipropionate, where it also has a prolonged action. We hope when used in the human being in the esterified form that it will not have these undesirable features.

SURGICAL TREATMENT OF BILATERAL POLYCYSTIC OVARIES—AMENORRHEA AND STERILITY*

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DURING the past ten years, we have particularly interested ourselves in patients whose principal complaints were amenorrhea and sterility and in whom we found bilateral polycystic ovaries. Partial oophorectomy by wedge resection was performed upon such patients with satisfactory results. In a previous paper (Stein and Leventhal[1]) on this subject, we reported 7 cases. We now desire to record the subsequent course in 6 of the 7 patients whom we were able to follow, and to report 21 additional cases. Patients who complained primarily of bleeding rather than of amenorrhea were omitted from this series even when the ovaries were involved. In many of the patients herein reported, menstruation was normal for a variable time after puberty, when irregularity developed. In some women, this was accompanied by excessive menstrual bleeding followed by increasingly extended intervals. This eventuated in a true amenorrhea which in several instances lasted from two to eight years. In some, particularly in single girls observed during adolescence, menstruation had never been definitely established with only occasional spotting prior to the development of amenorrhea. These varied symptoms were evidence of disturbed pituitary-ovarian relationship, resulting finally in amenorrhea and/or sterility. In this latter stage, both ovaries were found enlarged and polycystic. The symptomatology as observed in these patients, as well as anatomic characteristics of the ovaries, were fully described in the previous article.

PREVIOUSLY REPORTED SERIES

CASE 1.—M. G., first observed in October, 1928; aged 22 years; married 1½ years. *Irregular menses.* Hormone therapy failed. January, 1930, complained of *sterility* and *2 to 7 months' amenorrhea.* Pneumoroentgenogram revealed bilateral polycystic ovaries. May, 1930, bilateral wedge resection. Result: regular menses until October, when pregnancy occurred, with delivery at term. Menses normal and regular until February, 1933, when second pregnancy occurred; full term delivery. During 1937, laparotomy for gall bladder disease disclosed normal ovaries; no adhesions. Menstrual calendar records: 1937, 12 cycles; intervals of 28 to 31 days; 1938, 12 periods, 27 to 33 days. Last examination, April, 1938: no recurrence of cystic ovaries or amenorrhea—nine years postoperative (Fig. 1).

CASE 2.—B. K., August, 1931, aged 29 years; married 5 years. *Eight-year amenorrhea; five-year sterility.* Hormone therapy for one year prior to admission with no benefit. Hirsutism marked. Pneumoroentgenogram revealed bilateral polycystic ovaries. Bilateral wedge resection was followed by regular monthly periods

*Presented at a meeting of the Chicago Gynecological Society, March 17, 1939.

for 4 years when pregnancy occurred (1935); a second pregnancy occurred in 1936 with delivery at term of a 10-pound child. Menses have continued periodically. Menstrual calendar records: 1938, 9 cycles, 28 to 37-day intervals. Last examination, December, 1938; no recurrence of cystic ovaries or amenorrhea; eight years postoperative.

CASE 3.—L. C., April, 1929; aged 21 years, married 2 years. *Amenorrhea, 1 to 9 months, usually 6 months; sterility.* Hormone therapy for past 4 years. X-ray therapy to ovaries, December, 1929—no apparent effect. Repeated hormone therapy with some improvement and pregnancy, October, 1931. After delivery, secondary amenorrhea occurred and lasted 21 months in spite of hormone therapy. Examination revealed enlarged and tender ovaries and a pneumoroentgenogram in July, 1933, corroborated the findings. October, 1933: bilateral wedge resection was done and regular menses followed monthly. Two pregnancies and full-term deliveries in 1935 and 1938. Calendar record of menses: 1936, 10 periods at intervals of 27 to 39 days; 1938, 5 periods, 28 to 31 days. Last examination, August, 1938; no recurrence of cystic ovaries; 5 years postoperative.

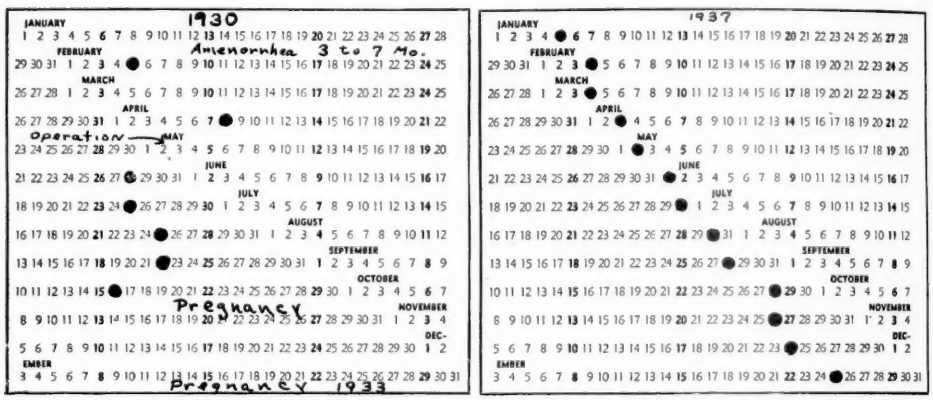

Fig. 1.—Case 1, M. G. Calendars of menstrual periods, showing establishment of regularity in 1937, after operation in 1930.

CASE 4.—H. W., January, 1933; aged 23 years, married 3 years. *Amenorrhea, 1 to 6 months, usually 3 or 4 months; sterility, 2 years.* Hormone therapy failed. On examination, the left ovary was found palpably enlarged and pneumoroentgenogram revealed that *both* ovaries were cystic. March, 1933: bilateral wedge resection. Regular menses for next 18 months; examination in March, 1934, revealed a normal pelvic status with no recurrence of cystic ovaries. In response to follow-up inquiry, it was learned that one pregnancy resulted.

CASE 5.—O. B., January, 1933; aged, 25 years, married 1½ years. *Irregular menses every 2 or 3 months; sterility.* Palpation revealed a cystic right ovary; pneumoroentgenogram showed *both* ovaries polycystic. Bilateral wedge resection performed, followed by regular monthly periods. Examination in September, 1934, and June, 1935, revealed no recurrence of the cystic ovaries. There was an additional male factor in the sterility picture; i.e., necrospermia. 1933: 11 cycles, 26 to 31-day intervals, usually 27; 1934: 11 cycles, 28 to 35 days, usually 29; 1935: 5 cycles to June, 26 to 31 days.

CASE 6.—E. A., October, 1933; aged 33 years, married 15 years. *Amenorrhea, 5 to 9 months with increasing intervals.* Both ovaries were palpably enlarged and cystic; these findings were verified by pneumoroentgenogram. Hirsutism and pain in the right lower quadrant were additional complaints. A bilateral wedge resection was performed and follow-up for eleven months revealed regular monthly periods and no recurrence of the cystic ovaries. No further follow-up response.

CASE 7.—M. B., August, 1933; single, aged 20 years. *Amenorrhea, 2 to 4 months; pain in both lower quadrants.* Rectal examination revealed both ovaries enlarged and cystic; these findings were corroborated by pneumoroentgenogram. Bilateral wedge resection was performed. The pain was relieved and regular menses were restored. Marriage a few months later, followed by regular periods. Menstrual calendars revealed: 1934: 9 cycles, 29 to 35-day intervals; 1935: 11 cycles, 28 to 34 days. Pregnancy, 1936, with delivery at term. Calendar record for the year following showed cycles of 30 to 34-day intervals. Last examined in July, 1937, at which time no recurrence of the cystic ovaries was found—5 years postoperative.

The results in these cases answer the objections of some gynecologists that partial ovarian resection is temporary in effect and is likely to be followed by recurrence. No recurrence has been observed in this series of patients, 5 of whom were followed from five to nine years postoperative. Furthermore, the fact that 5 of the 7 patients had 8 pregnancies subsequent to operation is testimony of restored fertility. One was lost sight of, and one with regular menses presented a male sterility factor. These women are enjoying good health (Fig. 2).

ADDITIONAL CASES

CASE 8.—E. A., July, 1935; aged 24 years, married 3 years. *Menses irregular, 1 to 2½ months; sterility, 3 years.* Following irregular bleeding, a tender mass was found in the left adnexae which led to the diagnosis of tubal pregnancy. At operation, a ruptured corpus luteum cyst with free blood in the peritoneal cavity was found. In addition, both ovaries were found to be polycystic. Bilateral wedge resection was performed. The next seven periods were reported to be of 29-day intervals. Examination showed no recurrence of cystic ovaries. Menstrual calendar for 1938: 27- to 32-day intervals, usually 29 days. Pathology (No. 1722): Hemorrhagic corpus luteum cyst; multiple follicle cysts; primordial follicles.

CASE 9.—M. E., February, 1937; aged 25 years, single. *Always irregular periods, usually 4 to 8 weeks; painful and often profuse.* Both ovaries cystic and tender on rectal palpation. Hormone therapy failed to relieve. Pneumoroentgenogram showed a small uterus and bilateral cystic ovaries. Dilatation and curettage and bilateral wedge resection performed April, 1937. Endometrium was in proliferating phase. From August, 1937, to December, 1938, 17 periods monthly at intervals of 27 to 35 days. Last examined in August, 1937, at which time there was a normal pelvic status with no recurrence of cysts. Pathology (No. 1083): Numerous follicle cysts; *Corpora albicantia;* fibrosis of ovary; moderately thick tunica; luteinized theca interna; old corpus luteum; secretory endometrium.

CASE 10.—H. E., September, 1935; aged 22 years, single. *Complained of seven months' amenorrhea.* Severe facial acne, marked hirsutism—masculine type. Rectal examination revealed both ovaries somewhat enlarged. Pneumoroentgenogram showed a small uterus and bilateral cystic ovaries. Hormone therapy for several months with no benefit. Pneumoroentgenogram repeated. Operation, February, 1936: hypoplastic uterus, both ovaries adherent, right containing a small chocolate cyst; both ovaries polycystic. Bilateral wedge resection including cyst area. Immediate improvement in patient's general health and complexion but no return of regular menses until 1938, when she had monthly periods of 19- to 36-day intervals. However, 7 of the 12 periods varied only 2 days. Last examined in June, 1937, at which time there was no evidence of recurrence of cystic ovaries. Pathology (No. 562): Endometriosis; mature Graafian follicle adjacent to follicle cyst; very thick tunica (the mature Graafian follicle is considerably below the surface); large follicle cysts; marked luteinization of theca interna.

CASE 11.—L. F., February, 1935, aged 31 years, married 2 years. *Complained of 4 months' amenorrhea and of sterility.* Hormone therapy of no benefit. Only

2 very scant periods from February, 1935 to October, 1936. Pneumoroentgenogram revealed a small uterus and bilateral polycystic ovaries. December 15, 1936: bilateral wedge resection performed, followed by irregular menses. Pregnancy six months later. Menses regular since; pelvic examination in February, 1938 revealed no evidence of recurrence of cystic ovaries. Second pregnancy, August, 1938. Pathology (No. 3222): Fibrosis of ovary; several large follicle cysts; thick tunica; luteinized theca interna.

CASE 12.—R. F., May, 1936, aged 28 years, single. *Complained of 2 months' amenorrhea,* and irregularity for past year. Marked hirsutism and obesity. Rectoabdominal findings indefinite. Complete metabolic work-up and x-ray of sella turcica were negative. Pneumoroentgenogram revealed bilateral cystic ovaries. Bilateral wedge resection performed in June, 1936. Uterus was small and both

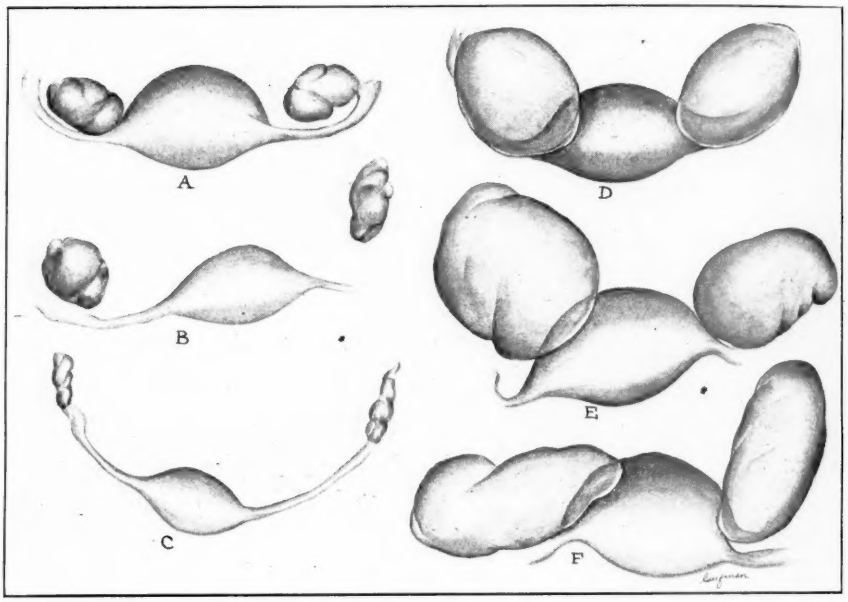

Fig. 2.—Comparative drawing illustrating the pneumoroentgenograms of *A*, Normal uterus and ovaries; *B*, uterine hypoplasia; *C*, fetal type uterine and ovarian hypoplasia; *D*, juvenile uterus, bilateral polycystic ovaries, Case 13; *E*, normal uterus, bilateral polycystic ovaries (large), Case 22; *F*, normal uterus, bilateral polycystic ovaries (oyster ovaries), Case 19.

ovaries polycystic. Following operation, menses were at intervals of 29 to 33 days, and in 1937, there were 11 periods, 31 to 40 days. Patient has left city. On written report, Jan. 1, 1938, patient is in good health and menstruating regularly. Pathology (No. 1530): multiple follicle cysts; atretic follicles; *Corpora albicantia;* luteinized theca interna.

CASE 13.—L. G., September, 1932, aged 14 years, single. *Menstruated every 3 months in past year.* Physical development masculine in type with marked hirsutism of face and body; breasts underdeveloped. Rectal palpation revealed a small uterus and indefinite adnexal findings. Pneumoroentgenogram in 1932 revealed a small uterus, and cystic ovaries. In June, 1933, she again complained of 2 to 3 months' amenorrhea and persistence of marked hirsutism. Second pneumoroentgenogram revealed cystic ovaries to be larger than on previous examination. Bilateral wedge resection, August, 1934. In 1936, periods were 21- to 27-day intervals, and in 1937, there were 12 periods of 19 to 28 days; in 1938, there were 11 periods at intervals of 25 to 34 days, but usually 27. Last examined in September, 1937: no recur-

rence of cystic ovaries. Marked improvement was noted in physical development. Breasts were developed, the hair on the face was of finer texture and much less noticeable; physical development was decidedly more feminine in type. Pathology (No. 1816): Multiple follicle cysts; no luteinization. Atrophic *Corpora albicantia;* marked proliferation of granulosa lining; normal tunica; numerous primordial follicles.

CASE 14.—M. G., April, 1935, aged 31 years, married 8 years. *Complained of sterility* and of very scant menses lasting but 1 day; regular in occurrence. Hirsutism of upper lip but otherwise feminine in type. Pelvic examination was negative. Pneumoroentgenogram in January, 1936, showed bilateral cystic ovaries and tubal obstruction. Repeat patency and pneumoroentgenogram in July, 1936, with same findings. Laparotomy, October, 1936. Both tubes were adherent but patent when tested from within; numerous small cysts were present in both ovaries. Bilateral wedge resection and lysis of adhesions were performed. Periods have improved in quality, now lasting 2 or 3 days. General health improved. In 1937, 11 periods of 23- to 26-day intervals, with one 32- and one 48-day interval. Last examined on Nov. 10, 1938, at which time there was no evidence of recurrence of cystic ovaries. Pathology (No. 3012): Beginning papillary adenofibroma on surface; several large follicle cysts; old corpus luteum; *Corpora albicantia;* recent atretic follicles; thick tunica.

CASE 15.—A. K., December, 1935, aged 23 years, married 1½ years. *Two to 3 months' amenorrhea; last period 3 months' ago; sterility.* Moderate obesity and hirsutism; masculine in type. Uterus 2 degrees retroverted; adnexa not palpable. Pneumoroentgenogram revealed the right ovary cystic; left was not visualized. Bilateral wedge resection on Feb. 19, 1936 for typical bilateral polycystic ovaries. In 1936, 10 periods, 27- and 34-day intervals, usually 29 or 30 days; 1937: periods regular, 28 to 31 days. Last examination, June, 1938: no change in hirsutism; pelvic examination revealed no recurrence of cystic ovaries. Report of urologist (Dr. A. E. Jones): Husband suffers from oligospermia. Pathology (No. 545): Luteinization of theca interna; several large follicle cysts; atretic follicles; thick tunica.

CASE 16.—E. H., September, 1937, aged 21 years, married 2 years. *Amenorrhea from 1 to 3 months; intervals becoming longer in past year.* Pain in both lower quadrants. Pelvic examination: Uterus normal in size, both ovaries cystic and tender. Bilateral wedge resection: typical bilateral polycystic ovaries. For next 9 months following operation, she menstruated at intervals of 31 to 37 days and has improved in general health. July, 1938, examination revealed no evidence of recurrence of cystic ovaries. Pathology (No. 2581): Numerous follicle cysts; thick granulosa layers; moderately thick tunica; fibrosis of ovary; atretic follicles; normal Graafian follicle.

CASE 17.—E. A., June, 1937, aged 16 years, single. Chief complaint: *amenorrhea.* Menstruated only twice since puberty. Marked hirsutism of male type which began at age of 12 and became more profuse; breasts underdeveloped. Rectal examination was negative. Pneumoroentgenogram showed a small uterus and both ovaries enlarged and cystic. Sella turcica was negative. X-ray showed no evidence of adrenal enlargement; metabolic studies were negative. Bilateral wedge resection performed in July, 1937. Patient menstruated on seventh postoperative day and again 34 days later. Amenorrhea of 4 months followed by periods at intervals of 32, 41, 43, and 121 days. Marked improvement in feminine development; breasts increased in size and facial hirsutism improved. Last examination in January, 1939: no recurrence of cystic ovaries. Pathology (No. 2070): Numerous follicle cysts; luteinization of theca interna; very thick tunica; many primordial follicles; follicle cyst undergoing luteinization of theca interna; old *Corpora albicantia.*

CASE 18.—R. B., October, 1938, aged 27 years, single. *Complained of 3 years' amenorrhea, 1934 to 1937, with pain in both lower quadrants.* Three months' amenorrhea prior to admission. Obesity, hirsutism of face, arms and legs—masculine in type. Rectal examination unsatisfactory. X-ray showed no evidence of adrenal tumor; sella turcica was negative. Pelvic pneumoroentgenogram showed the

right ovary enlarged and cystic; the left ovary was not visualized. At laparotomy both ovaries were typically polycystic. A bilateral wedge resection was performed. Postoperative examination in February, 1939, showed no recurrence. Had three menstrual periods since operation (4 months previously). Pathology (No. 3000): Fibrosis of ovary; *Corpora albicantia;* atretic follicles; few follicle cysts; tunica very thick.

CASE 19.—V. M., June, 1937, aged 22 years, single. *Amenorrhea of 14 months' duration.* Rectal palpation unsatisfactory. Pneumoroentgenogram showed bilateral cystic ovaries; bilateral wedge resection was done in September, 1937. Patient menstruated 3 days after operation. Last examined in February, 1938: no recurrence of cystic ovaries. Reported monthly periods of 20- to 26-day intervals. Pathology (No. 2705): Corpus luteum; many follicle cysts; primordial follicles.

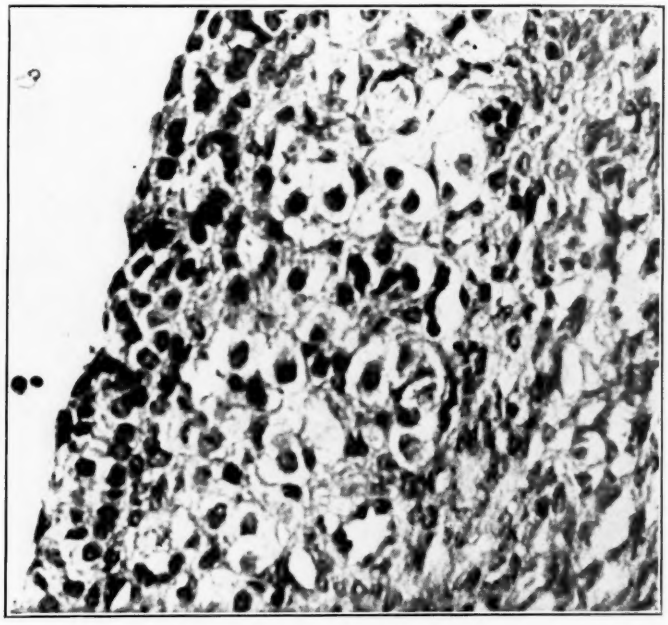

Fig. 3.—Case 20. Wall of follicle cyst showing several layers of granulosa cells and luteinized theca interna layer. ×400.

CASE 20.—V. H., February, 1935, aged 23 years, single. *Irregular periods, 3 to 8 weeks, last period 2 months previously; pain in right lower quadrant.* Tender left ovary found in the cul-de-sac. Hirsutism marked. Exploratory laparotomy revealed bilateral polycystic ovaries and adherent appendix. Typical bilateral wedge resection and appendectomy performed. Following operation, periods were regular at 30- to 33-day intervals. In 1937, 12 periods of 25 to 31 days; in 1938, 12 periods, 24 to 32 days, usually 27. Last examined in February, 1939 at which time there was no recurrence of cystic ovaries; general health improved. Pathology (No. 265): Follicle cysts; no luteinization; several growing follicles; fairly thick tunica; large amount of theca externa in follicle cysts; thick theca interna; proliferating granulosa layer of cysts.

CASE 21.—M. M., December, 1935, aged 19 years, single. *Complained of amenorrhea.* Spotted 3 times in past 6 years; no regular menses. Profuse growth of coarse hair on cheeks and upper lip. Rectal examination unsatisfactory. Pneumoroentgenogram showed a small uterus and bilateral cystic ovaries. Bilateral wedge resection February, 1936, followed by menses in March, May, June, and July. Examination in June, 1937 showed no recurrence of cystic ovaries, the

uterus appeared somewhat larger, facial hirsutism was improved and the breasts were developed. Patient reported she was menstruating regularly; failed to return menstrual calendars for 1937 and 1938. Pathology (No. 394): Tunica very thick; granulosa cells luteinized; beginning atretic follicles with luteinization of theca interna; many large follicle cysts.

CASE 22.—P. P., May, 1937, aged 23 years, married. *Complained of 2 months' amenorrhea;* always irregular. Uterus small, tender cystic mass behind the uterus. Pneumoroentgenogram showed bilateral cystic ovaries. Bilateral wedge resection; periods regular every 31 to 32 days after operation. Patency test, March, 1938 followed by pregnancy and delivery at term. Postnatal examination, March, 1939 revealed normal pelvic status with no recurrence of cystic ovaries. Pathology (No. 1387): Many follicle cysts; fairly thick tunica; many *Corpora albicantia.*

CASE 23.—G. S., August, 1929, aged 23 years, married. *Complained of a 3 months' amenorrhea.* Bilateral cystic ovaries on palpation confirmed by pneumoroentgenogram. Laparotomy: right dermoid cyst and left polycystic ovary. Bilateral wedge resection, following which for 6 years, periods were regular at 30- to 32-day intervals. Patient practiced contraception during this time. Upon omitting same, she promptly conceived (March, 1935) and delivered at term. Examination in November, 1937 showed a normal pelvic status with *no recurrence of cysts—8 years after resection.* Menses every 28 to 35 days in 1937, and in 1938, 28- to 34-day intervals, with one interval of 43 days. Pathology (No. 1331): Right ovary, many *Corpora albicantia;* follicle cysts; dermoid cyst; left ovary, numerous follicle cysts; normal tunica.

CASE 24.—L. S., September, 1936, aged 23 years, married 3 years. *Complained of 2 years' amenorrhea.* Hormone therapy of no benefit. Slight hirsutism. Pelvic findings indefinite. Pneumoroentgenogram showed bilateral cystic ovaries with globular right ovary. Subsequent examination followed by vaginal bleeding; second pneumoroentgenogram revealed diminution in size of globular swelling on right. Both ovaries were still cystic. Wedge resection was performed. Regular periods every 26 to 29 days, usually 27, through 1936 and 1937. Pregnancy occurred in December, 1937, with delivery at term. Postnatal examination, October, 1938: no evidence of recurrence of cystic ovaries. Pathology (No. 2692): Numerous follicle cysts; luteinized theca interna; *Corpora albicantia;* atretic follicles; primordial follicles; thick tunica; corpus luteum.

CASE 25.—S. W., July, 1935, aged 23 years, married 2½ years. *Complained of sterility* with somewhat irregular periods. Unsatisfactory pelvic findings. Pneumoroentgenogram revealed bilateral cystic ovaries. Bilateral wedge resection performed, following which periods were every 24 to 28 days. Last examination, August, 1936: normal pelvic status with no recurrence of cystic ovaries. Male sterility factor: Failure of intromission; unsuccessful operation for hypospadias. Pathology (No. 1048): Luteinization of theca interna; numerous follicle cysts; fairly thick tunica; many atretic follicles; few *Corpora albicantia;* primordial follicles.

CASE 26.—M. W., July, 1935, aged 28 years, married 6 years. *Complained of sterility and irregular periods with 2 months' amenorrhea.* Left ovary palpably enlarged and tender. Pneumoroentgenogram showed bilateral cystic ovaries. After typical wedge resection, patient had four periods at intervals of 28, 29, 34, and 48 days, and then became pregnant with delivery at term. Postnatal examination showed no recurrence of cystic ovaries. In 1937, patient had 7 periods, 28- to 33-day intervals; in 1938, 28 to 36 days, with one interval of 46 days. Pathology (No. 36P44): Corpus luteum with hemorrhage; many *Corpora albicantia;* fibrosis of ovary; atretic follicles with luteinization of granulosa and theca interna cells; marked proliferation of theca cells; normal tunica.

CASE 27.—A. M., May, 1931, aged 24 years, married 3 years. *Complained of sterility and amenorrhea of 2 years and 8 months;* always irregular and scant. Two previous periods of amenorrhea each lasting one year. Pain in right lower quadrant,

hirsutism of face, male type, and slight obesity. Examination showed a normal uterus and typical bilateral polycystic ovaries. Bilateral wedge resection, Gilliam suspension and appendectomy were performed. Periods every 2 to 4 weeks followed and pregnancy occurred April, 1937. Porro cesarean section performed at term for severe intra-partum infection. Pathology (No. 983): Fibrosis of ovary; atretic follicles; numerous follicle cysts; *Corpora albicantia;* normal tunica; one apparently normal maturing Graafian follicle surrounded by markedly proliferating theca interna.

CASE 28.—B. R., November, 1935, aged 27 years, married. *Complained of amenorrhea of 9 months to one year.* Pelvic examination showed a small uterus, right ovary palpably enlarged and cystic; left ovary not palpable. Slight obesity. Pneumoroentgenogram showed bilateral cystic ovaries. Dilatation and curettage and typical bilateral wedge resection performed. Menses on third postoperative day.

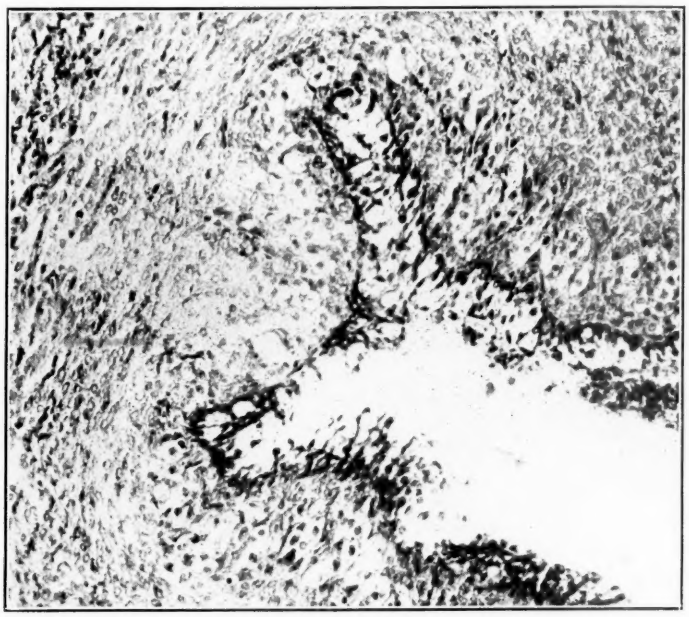

Fig. 4.—Case 26. Atretic follicle, marked luteinization of theca interna, early luteinization of granulosa layer. ×140.

Postoperative examination, Dec. 5, 1935: no recurrence of cystic ovaries. Did not return for follow-up. Pathology (No. 2840): Proliferating endometrium; number of follicle cysts with fairly thick tunica; atretic follicles; luteinized theca interna (Table I).

For the past three years, all of these patients were given menstrual calendar cards and each year the collected cards were exchanged for new ones; hence an accurate menstrual record was obtained. A study of these records reveals that while none of the patients menstruated at exactly twenty-eight-day intervals, they had recurring cycles within the normal variation. This observation is in complete accord with the results of our study of several hundred calendar records obtained from our clientele. We found that none of our patients were entirely regular, but that variations of 4 to 6 days were usual, and wide variations not infrequent in women who claimed to menstruate regularly.

TABLE I. CASE ANALYSIS

NO. CASES	STATUS	AMENORRHEA	STERILITY	PALPABLE CYSTIC OVARIES	PNEUMOROENTGENOGRAM	HIRSUTISM	PAIN	HORMONE TREATMENT
10	Single	9		3—both 1—one 6—none	9	7	2	1
18	Married	16	14	5—both 6—one 7—none	15	8	5	7

PATHOLOGY

The pathology in the 21 additional cases was found to follow a similar pattern to that described in our previous publication. Grossly, each ovary was enlarged 4 to 5 times and was either elongated or globular, and contained numerous small cysts in the cortex. The capsule was thick and leathery with variations in thickness in different portions of the section. Occasionally, a larger follicle cyst found protruding from the surface of the ovary was covered by a thin capsule, giving the ovary a lobulated appearance. Upon section of the ovary, a clear fluid was released under pressure from numerous small cysts measuring from 2 to 15 mm. in diameter. Usually these cysts were limited to the cortex but in some instances involved the hilus. Not infrequently, a corpus luteum cyst was found in addition.

Microscopically, the most characteristic finding is the numerous follicle cysts. In our previous publication, we differentiated between theca-lined and granulosa-lined cysts, but we now believe this differentiation to be of no significance. The smaller cysts are all lined with multiple layers of granulosa cells. As the cysts enlarge, the granulosa lining becomes thinned out until but a single layer is present. The largest cysts seem to have lost the granulosa layer. This may either be due to an artifact in sectioning or to actual pressure atrophy. However, physiologically, the theca cells as well as the granulosa cells are estrin-producing so that the actual differentiation between such cysts is of no clinical importance.

A thick fibrous capsule is characteristic and is usually associated with increased fibrosis of the ovary and hyperplasia of the theca layers. The latter is most evident surrounding the atretic follicles which are observed to be more numerous than in the normal ovary. Robinson[2] called attention to the presence of luteinization of the theca interna of such atretic follicles and stated that this was a characteristic finding in patients with metrorrhagia. Further study of our sections reveals that it is equally characteristic in the ovaries of our patients with amenorrhea. The luteinization not only involves the theca interna but occasionally the granulosa layer of atretic follicle cysts as well (Figs. 3 and 4). We have no knowledge as to whether such luteinized cells are capable of producing progesterone. Table II is a detailed analysis of the sections in each case of this series.

TABLE II. PATHOLOGY

CASE	THICK TUNICA	GRAAFIAN FOLLICLES	FOLLICLE CYSTS	CORPUS LUTEUM	CORPORA ALBICANTIA	LUTEINIZED THECA	OTHER FINDINGS
8	Normal	++	++	Cyst	0	0	
9	+	0	++	Old	+	+	Fibrosis
10	++	+	++	0	0	++	Endometriosis
11	++	0	++	0	0	+	Fibrosis
12	Normal	0	++	0	++	+	
13	Normal	++	++	0	++	0	
14	++	0	++	Old	+	0	Papillary adenofibroma
15	++	+	++	0	0	+	
16	++	++	++	0	0		Fibrosis
17	++	++	++	0	Old	+	
18	++	0	+	0	+	0	Fibrosis
19	Normal	++	++	Cyst	+	0	
20	+	++	++	0	0	0	Proliferating theca interna
21	++	0	++	0	0	+	
22	+	0	++	0	++	0	
23	Normal	0	++	0	++	0	Dermoid
24	++	++	++	Old	+	+	
25	+	++	++	0	+	+	
26	Normal	0	++	Hemorrhagic	++	++	Fibrosis
27	Normal	+	++	0	+	0	Fibrosis
28	++	0	++	0	0	+	

TREATMENT

Amenorrhea is a symptom and as such is evidence of the disturbed physiologic function of the sex apparatus. In the early stages, it may be due to hormonal disturbances in which no definite pathologic lesion may be demonstrated in the sex organs. In fact, both amenorrhea and uterine bleeding, according to B. Zondek,[3] are due to the same fundamental process; namely, a hypersecretion of the anterior lobe of the pituitary gland. When, however, in the opinion of the authors, such dysfunction persists for a long time, histologic evidence appears in the ovary in the form of multiple follicle cysts varying in size from a few millimeters to more than one centimeter. When this pathologic change has occurred, amenorrhea and sterility are the chief symptomatic characteristics and pain is an occasional accompaniment.

Many contributions have appeared in the literature on the medical and surgical treatment of ovarian dysfunction. It is our belief that the good results reported from medical management, such as glandular and radiation therapy, have been obtained in patients in whom the ovarian dysfunction is still in the stage where no demonstrable enlargement of the ovary is found. Since none of the reports of successful treatment by these methods include patients in whom definite polycystic ovaries were demonstrated, those conditions must be regarded as purely dysfunctional. It seems evident, then, that patients who have failed to respond to medical treatment and have developed definite pathologic lesions in the ovary require surgical intervention.

Medical Management.—Hormone therapy has been employed in the past few years for early dysfunction exhibiting amenorrhea and often associated with sterility, but with very disappointing results. Estrogenic substances have been employed, but according to Frank,[4] they serve no useful purpose in this condition. The pregnancy urine extract has likewise been used with unsatisfactory results. We question whether therapy with pregnancy urine extracts, mare's serum hormone and extracts of the anterior lobe of the hypophysis is justified for these conditions, for not only are they of dubious value, but may actually intensify the pathologic change in the ovary. In cases of hypothyroidism associated with sterility, thyroid extract has been shown to be of definite therapeutic value. Tamis[5] declares that a combination of thyroid and roentgen therapy is the best agent for stimulating menstruation in cases of functional amenorrhea and in 60 per cent of his 25 cases, the menses were restored by this means.

Perhaps one of the most useful forms of medical treatment of functional amenorrhea and sterility is radiation therapy, which Rubin[6] recommended in 1926, when he reported a successful series of cases. More recently, Kaplan,[7] basing his opinion on his experience with 128 women so treated over a period of twelve years, declared that no other method of treatment so far devised, including hormone therapy, has yielded results as satisfactory or equally as good. In 76 patients, the menses were regulated by treatment and 52 failed to respond; all of the patients had previously been treated with endocrine preparations without success. Radiation was applied to the ovaries in all cases, to the pituitary as well in 80, and in 5, to the thyroid also. Forty-four women became pregnant, giving birth to 47 living children. Kaplan was able to follow up 114 of his patients. However, there is no detail concerning postradiation pelvic examination to determine whether palpable ovarian pathology developed; nor is there evidence in this report that any of the patients so treated had bilateral polycystic ovaries prior to radiation therapy.

Mazer and Spitz[8] likewise used low dosage radiation in the treatment of 48 women complaining of secondary amenorrhea, 22 of whom menstruated regularly for one year or more thereafter. Of the 103 sterility patients so treated, 22 conceived. The authors state, however, that but 38 of the women were married to fertile mates.

Friedman and Seligman[9] treated 9 cases of amenorrhea, diagnosed as basophilic adenoma of the hypophysis, with x-ray of the pituitary and ovary; there was restoration of the menses in all and occurrence of pregnancy in 3 cases. Likewise, in these cases there is no evidence that any of the foregoing had polycystic ovaries prior to treatment.

It is erroneous to call x-ray a stimulating agent, for its action is always destructive, according to Tamis;[5] destruction of the inhibitory forces results in stimulating effects. Israel[10] declares that while radiation is purely an empiric measure, it is safe in experienced hands. It is our opinion that the favorable results which have been obtained with roentgen therapy have occurred in cases of endocrine dysfunction which have not yet reached the stage where fixed changes have taken place in the ovary.

No one has reported treating polycystic ovaries with x-ray. When both ovaries are found to be polycystic, either upon pelvic bimanual or roentgen visualization, we believe that surgical treatment is indicated.

Surgical Treatment.—Since our previous report on this subject in 1934, there have been a number of interesting papers bearing on the surgical treatment of bilateral polycystic ovaries. All of these communications have been based upon the same principle, namely, the removal of a portion of the cystic cortex or evacuation of the cystic follicles. However, different techniques have been employed for this purpose with uniformly good results.

Bailey[11] in 1937 described the operation of "extroversion of the ovary for functional amenorrhea" and reported his results in 17 patients observed over a period of six years. All of his patients had previously been treated with hormone therapy without improvement. He therefore removed a wedge of each ovary and sutured each half of the slit gonad so that it remained wide open and turned the raw surfaces into the cul-de-sac to prevent adhesions. He declared that no complications

resulted from this procedure and that in 13 of the 17 patients, regular menses were established. Pregnancy resulted in one case. Bailey believed that the pathologic change which occurs in the ovary is a result of the presence of a basic pituitary hormone deficiency; that lack of the follicle ripening and ovulation leads to development of multicystic disease with chronic thickening of the tunica; that the more mature follicles are probably destroyed intrinsically or by pressure obliteration, and the younger, deeper ones are mechanically prevented from reaching the surface to mature and ovulate. This interpretation of the mechanics involved in the lack of ovulation is in accord with the view expressed in our previous communication. The technique which he employs attempts to assist to maturity the remaining follicles by facilitating their approach to the surface. A single ovulation, he states, is capable of re-instating the normal ovular rhythm. He justifies the operation with the belief that when the pathologic condition can be diagnosed, the prospect of a spontaneous return to normal function is remote, inasmuch as the lesion is a progressive one. We are in accord with the principles involved in Bailey's mode of therapy, disagreeing only with the technique which he employs.

Robinson,[2] after prolonged study, was convinced that patients suffering from hypo- or hyperfunction of the ovary for long periods will present, on careful bimanual examination, enlargement of one or both ovaries. If endocrine therapy and dilatation and curettage have failed to relieve bleeding, ovarian partial resection is indicated. He reports 4 such cases, utilizing a technique of wedge resection and suture similar to that described by us. Normal menses were restored in all 4 patients and pregnancy resulted in 2. He likewise reported 3 cases of amenorrhea treated by the same method, in which the menses were successfully regulated, with pregnancy occurring in 2. In both conditions he concludes that removal of the cystic cortex of the ovary restores the normal pituitary-ovarian relationship. Robinson enters into a thorough discussion of this involved endocrine problem which may be reviewed with profit.

Reyeraft,[12] after encountering disappointing results with endocrine treatment, noted the gratifying effects of wedge resection reported by Robinson, and utilized this principle in treating 6 cases. He, however, modified the technique by performing a "decortization" of the ovary rather than a wedge resection, believing that the thick tunica was the significant barrier to ovulation. After removing a portion of the ovarian cortex, he obtained hemostasis by means of a mattress suture of fine catgut, leaving the ovaries denuded of their normal covering. He obtained restoration of the menstrual function in 5 of the 6 cases of amenorrhea, and pregnancy resulted in one case.

Stein and Leventhal[1] in 1935 reported 7 cases of amenorrhea associated with bilateral polycystic ovaries in whom bilateral wedge resection was performed. A large wedge of from one-half to two-thirds of the ovarian cortex was removed and the deeper cysts in the remaining portion of the ovary were punctured. The ovary was then closed by means of a single suture of fine catgut in two layers, the first, a deep hemostatic stitch locked at either end, and returned as a superficial approximating suture. This left an ovary of approximately normal size and appearance. There was restoration of the menses in all of the 7 patients, pregnancy occurring in 5 patients, twice in 3 of them. A follow-up on 6 of the 7 patients was obtained by the present authors and appears in the history abstracts above.

We desire to add to this group 21 patients, all of whom complained of amenorrhea and/or sterility, and in whom bilateral ovarian enlargement was either found by palpation or demonstrated by pneumoroentgenography. As will be seen in Table III, the combined series consists of 10 single and 18 married women. Postoperatively, regular menses were restored in 23; irregular periods occurred in 2, and follow-up was unsuccessful in 3. One single girl in the first series was subsequently married and gave birth to a child at term. In addition to this case, 10 of the married group became pregnant, 4 of them twice. These patients were followed to date by means of menstrual calendar records and periodic pelvic examinations. No recurrence of cystic ovaries was detectable upon postoperative and follow-up examination in any case, 7 patients having been followed for more than five years (3, 5 years; 3, 8 years; 1, 9 years) (Table III). It would be desirable for scientific purposes

to substantiate, by follow-up, the bimanual findings with pneumoroentgenograms as was done preoperatively. However, as these patients were all in good health, menstruating regularly, many of them having borne children, there was no justification from the standpoint of the patient for the additional expense and inconvenience. All of these patients are now in good health and calendar records of their menses are recorded in the case histories above.

Many surgeons are accustomed to treating polycystic ovaries incidentally found at laparotomy by multiple puncture of the follicle cysts. Recently, Zondek[3] has advocated the performance of such multiple puncture through the cul-de-sac, thus obviating the necessity for laparotomy. He reported success with 40 cases.

TABLE III. RESULTS

NO. CASES	STATUS	AMENORRHEA	STERILITY	MENSES—P.O.		NO. PTS. PREGNANT	TOTAL PREGNANCIES	RECURRENCE
				REG.	IRREG.			
10	Single	9		7	1 2†	1*	1*	0
18	Married	16	14	16	1 3†	10§	14	0‡
28		25	14	23	2	11	15	0

*Married 4 months after operation.
†No follow-up.
‡7 cases followed 5 to 9 years without recurrence.
§8 of 10 patients complained primarily of sterility.

Although four separate surgical methods of treating polycystic ovaries have been described, it is noteworthy that success in restoring the physiologic function of the ovary was obtained in each. It is obvious that the good results were due to the removal of cortical follicle cysts—the significant lesion in the relationship between polycystic ovaries and the dysfunction. While the methods varied, the results were uniformly good. In our opinion, Zondek's cul-de-sac puncture of the follicle cysts appears to be too inadequate and uncontrolled for general use. The procedures of both Bailey and Reycraft, based on the assumption that the thick tunica is the significant barrier to ovulation, leave the ovaries denuded of their normal epithelium, thus inviting postoperative bleeding and adhesions. On the other hand, wedge resection and suture, which was described by the authors and also employed by Robinson, is a complete surgical technique which restores the normal anatomy of the ovary. Contrary to a common prejudice, this operation is not followed by recurrence.

SUMMARY AND CONCLUSIONS

1. During the past ten years, we have operated upon 28 patients with bilateral polycystic ovaries in whom amenorrhea and/or sterility were the chief characteristics.

2. Pneumoroentgenography was found to be of distinct value in diagnosis. Bilateral ovarian enlargements were demonstrated by this means in cases where pelvic examination was unsatisfactory and was corroborative in others. This form of x-ray diagnosis was employed in 24 of our 28 cases.

3. Bilateral partial oophorectomy by means of wedge excision and suture was found to be a satisfactory technique.

4. The calendar method of recording menstrual cycles was utilized in all of these patients in the past three years so that accurate data are available.

5. Menstruation was restored in 25 of the 28 women and in 3 there was no follow-up. Of 19 married women (one single when operated upon and subsequently married), 11 became pregnant, with a total of 15 pregnancies. In this group were 14 who complained primarily of sterility and of these, 8 became pregnant.

6. Follow-up pelvic examinations were made routinely and no case of recurrent cystic ovaries has been observed. Seven patients have been followed for from five to nine years since operation.

7. On the basis of our long period of study of this condition, and the results obtained in the 28 women herein reported, we recommend that surgical treatment be considered the method of choice for bilateral polycystic ovaries associated with amenorrhea and/or sterility. The technique of partial oophorectomy by wedge resection and suture is advocated.

We wish to express our gratitude for assistance in the preparation of the material for this paper to Drs. M. L. Leventhal and Otto Saphir.

REFERENCES

(1) *Stein, I. F., and Leventhal, M. L.:* Am. J. Obst. & Gynec. **29:** 181, 1935. (2) *Robinson, M. R.:* Ibid. **30:** 18, 1935. (3) *Zondek, B.:* Harefuah M. J. **14:** 12, 1938. (4) *Frank, R. T., Goldberger, M. A., Salmon, U. J., and Felshin, G.:* J. A. M. A. **109:** 1863, 1937. (5) *Tamis, A. B.:* Am. J. Obst. & Gynec. **32:** 845, 1936. (6) *Rubin, I. C.:* Ibid. **12:** 76, 1926. (7) *Kaplan, I. I.:* Ibid. **34:** 420, 1937. (8) *Mazer, C., and Spitz, L., Jr.:* Ibid. **30:** 214, 1935. (9) *Friedman, A. B., and Seligman, B.:* Radiology **29:** 99, 1937. (10) *Israel, S. L.:* Endocrinology **22:** 253, 1938. (11) *Bailey, K. V.:* J. Obst. & Gynaec., Brit. Emp. **44:** 637, 1937. (12) *Reycraft, J. L.:* Am. J. Obst. & Gynec. **35:** 505, 1938.

DISCUSSION

DR. JOHN I. BREWER.—I believe that the paper demonstrates that surgical procedure is of value in certain cases of amenorrhea. The long follow-up shows that surgical removal of some ovarian tissues in these instances does cause improvement. We have operated upon 6 such patients in the last five years. Of these 6 one is two months pregnant at the present time.

In contrast to Stein and Cohen's paper in which the treatment described is for secondary amenorrhea, we have one patient, 22 years old, who had a primary amenorrhea and who after extensive endocrine therapy failed to flow. By extensive therapy, I mean 200,000 to 300,000 units of theelin in three weeks and 30 mg. of proluton in ten days. This patient was found at operation, not to have polycystic ovaries but fibrous appearing ovaries. These were biopsied by a technique similar to the authors' and demonstrated small cystic follicles, none of which contained ova. Most of them showed luteinization of the theca without luteinization of the granulosa. Three days following curettage in which very little endometrial tissue was obtained, the patient flowed for two days. She was operated upon in 1934, and in the five years since has menstruated every month with one exception of a sixty-day period of amenorrhea. As for the other four patients we have had, they have improved but since all four are single we have no data as to sterility.

Other methods of treatment that have been suggested, such as puncture of the cysts and vaginal massage of the ovaries, have one feature in common, trauma. Such trauma would certainly increase the blood supply, which physiologically any organ needs for increased function.

Another probable factor is the estrogenic concentration. It has been demonstrated experimentally that certain maintained levels of estrogenic substance can produce ovarian inactivity, presumably by way of the pituitary. If this quantitative level is changed, then menstruation ensues. The work done by Stein and Cohen suggests that it is the change in quantitative estrogenic level that brings about more normal menstruation.

In conclusion, I wish to say, as the authors have stressed, that this procedure is not a cure-all for amenorrhea or sterility. In other words, every patient with amenorrhea and sterility should not be operated upon. The operation should be done only in selected instances.

DR. EDWARD ALLEN.—I would like to report a further case. This patient was 24 years old and had never menstruated. She was very masculine, with large clitoris which she came to have removed. The ovaries were less than one-third normal size and the uterus so small that you could hardly tell whether you were feeling a wedge of peritoneum. I removed a wedge from each ovary. Whereas, when we first examined her you could not put the smallest probe in the cervix, within three weeks a Hegar dilator could be passed. She has since married, and the uterus is now two-thirds normal size.

Certainly this set of ovaries has very little follicular activity, which brings up the question of puncturing through the cul-de-sac. By puncturing through the cul-de-sac you can cut down on the hospitalization and discomfort. I have resected two cases in the last year through the cul-de-sac, which were of the polycystic type. I think it is important to consider this method and rather than treat too few, treat more of these cases surgically.

DR. A. M. SCHWITTAY, MADISON, WIS.—I would like to ask whether in these cases basal metabolism determinations have been done. It is our experience that in many amenorrheic cases there is a low basal metabolism. We have found in many young girls, particularly those who have menstruated for a time and then have amenorrhea, a deficient thyroid is at fault.

DR. M. L. LEVENTHAL.—In the past year I have had occasion to operate upon three cases with polycystic ovaries, to study the endometrial biopsies, and to take basal metabolic rates. I found in all three that the biopsy showed a preovulatory or a proliferative endometrium. In two of the cases that were typically polycystic, in that they had long periods of amenorrhea and menstruated normally after operation, the basal metabolic rates were normal. In one it was minus 31. This patient was given intensive thyroid therapy and the basal metabolic rate came up to minus 1 and still she did not menstruate. In this patient only by pneumoperitoneum were we able to discover the polycystic ovaries. We operated upon these two patients and both menstruated within the month, one on the twenty-eighth and one on the twenty-ninth postoperative day. I think the role of hypothyroidism in amenorrhea is important, but not in the presence of these organic changes in the ovary.

DR. COHEN (closing).—There are many theories concerning the cause of polycystic ovaries. Of these, two merit attention, namely, the mechanical theory wherein the thickened tunica albuginea prevents follicle rupture, and the theory of hyperpituitarism. In animals, anterior pituitary extracts and implants, anterior pituitary-like hormone, as well as the mare serum hormone will produce cystic ovaries. In the human being, mare serum hormone in large doses will produce cystic ovaries. In the newborn infant, Spivack reported the occurrence of cystic ovaries, produced perhaps by the high level of maternal prolan. Cushing and Kraus have reported cases of increased intracranial pressure associated with polycystic ovaries. The finding of polycystic ovaries at prepuberty and menopause may be considered physiologic. Perhaps in the menopause the increased prolan A might be a factor.

The occurrence of amenorrhea may be explained by the failure of follicle rupture because of mechanical crowding. The estrin produced by follicle cysts may produce

anterior pituitary inhibition. Moreover, progestin produced by corpora lutea, corpus luteum cysts, or possibly from luteinized atretic follicles (false corpora lutea) would produce amenorrhea.

In answer to Brewer's statement about vaginal trauma producing pelvic hyperemia, it seems to us more logical to suppose that it would produce follicle rupture and thus cure the amenorrhea.

Allen suggested cul-de-sac resection. We have felt that the cul-de-sac route was not safe because of the great possibility of hemorrhage and therefore in all of our cases, we used the abdominal route.

FAMILY TRENDS ACCORDING TO ECONOMIC STATUS

CHARLES P. SHELDON, M.D., BOSTON, MASS.

ALTHOUGH human fertility is altered by social status, occupation, urbanization, education, religion, biologic factors, etc., the economic situation is of considerable importance in determining the size of a family. We have witnessed during the past several years the effects of an economic depression during which large numbers of persons have had their mode of living disrupted. Family incomes are in many instances low and the relief rolls are enormous. The social implications of this situation are brought out by a study of fertility rates in groups of persons of varying economic levels.

FERTILITY RATES

The present study is based upon records of 964 women who were delivered at the Albany Hospital, Albany, New York, in the years 1931 to 1935 inclusive. These were subdivided in three main groups. The service group was made up of city and ward patients who were largely supported by public funds. A semiprivate group consisted of patients of moderate means. The private group was made up of persons who were financially independent. The patients were from rural as well as urban districts.

Table I shows the number of pregnancies these women have had. The average number of pregnancies for the three groups combined was 2.4. Those in the service group (city and ward) had an average of 3.4 pregnancies and those in the self-sustaining group (semiprivate and private) had an average of 2 pregnancies.

TABLE I. PREGNANCY INCIDENCE ACCORDING TO ECONOMIC STATUS

TYPE OF SERVICE	NUMBER OF MOTHERS	NUMBER OF PREGNANCIES	AVERAGE NUMBER OF PREGNANCIES
Total	964	2,314	2.4
City and ward	262	895	3.4
Semiprivate	376	775	2.1
Private	326	644	2.0
Private and semiprivate	702	1,419	2.0

In order to eliminate the differences of age in the various groups, calculations were made for the number of months each woman could have

become pregnant.[1] This number of months was obtained by determining the interval between marriage and last delivery and subtracting 10.5 months for each live or stillbirth. Miscarriages and abortions were adjusted by subtracting the number of months pregnant plus 1. On this basis Table II was constructed, showing that although the average interval between delivery and succeeding pregnancy for the service group was only 12.5 months, the interval for the self-sustaining group was 22.4 months.

TABLE II. PREGNANCY RATES ACCORDING TO ECONOMIC STATUS. CALCULATIONS BASED ON EXPOSURE TO PREGNANCY

TYPE OF SERVICE	NUMBER OF MONTHS OF EXPOSURE TO RISK OF PREGNANCY	NUMBER OF PREGNANCIES	AVERAGE INTERVAL BETWEEN DELIVERY AND SUCCEEDING PREGNANCY (MONTHS)
Total	42,968	2,314	18.6
City and ward	11,206	895	12.5
Semiprivate	16,799	775	21.7
Private	14,963	644	23.2
Private and semiprivate	31,762	1,419	22.4

The statistics of this study are substantiated by similar investigations which reveal an inverse relationship between economic status and differential fertility.[2, 3]

Although fertility apparently increases as social status and the family income diminish, there are other factors which influence the size of a family. Reproductive wastage counteracts fertility and tends to increase, both in the individual and in the group, with an increase in fertility.

PREGNANCY WASTAGE

Tables III, IV, and V give the number of abortions, miscarriages and stillbirths and the rates for each per 1,000 pregnancies in the three groups. The rate in each case is much higher for the service group than for the self-sustaining group.

TABLE III. ABORTION RATES ACCORDING TO ECONOMIC STATUS

TYPE OF SERVICE	NUMBER OF PREGNANCIES	NUMBER OF ABORTIONS	NUMBER OF ABORTIONS PER 1,000 PREGNANCIES
Total	2,314	179	77.4
City and ward	895	81	90.5
Semiprivate	775	45	58.1
Private	644	53	82.3
Private and semiprivate	1,419	98	69.1

The total effect of reproductive wastage is shown in Table VI in which abortions, miscarriages, and stillbirths are added together and the rates per 1,000 pregnancies given.

The survival of children is of equal importance with the rate at which they are born. Although the infant mortality rate in the service group was 94.6, the rate for the self-sustaining group was only 40.9, which is less than one-half the rate for the service group.

TABLE IV. MISCARRIAGE RATES ACCORDING TO ECONOMIC STATUS

TYPE OF SERVICE	NUMBER OF PREGNANCIES	NUMBER OF MISCARRIAGES	NUMBER OF MISCARRIAGES PER 1,000 PREGNANCIES
Total	2,314	39	16.9
City and ward	895	22	24.6
Semiprivate	775	11	14.2
Private	644	6	9.3
Private and semiprivate	1,419	17	12.0

TABLE V. STILLBIRTH RATES ACCORDING TO ECONOMIC STATUS

TYPE OF SERVICE	NUMBER OF PREGNANCIES	NUMBER OF STILLBIRTHS	NUMBER OF STILLBIRTHS PER 1,000 PREGNANCIES
Total	2,314	57	24.6
City and ward	895	27	30.2
Semiprivate	775	16	20.6
Private	644	14	21.7
Private and semiprivate	1,419	30	21.1

TABLE VI. PREGNANCY WASTAGE RATES ACCORDING TO ECONOMIC STATUS

TYPE OF SERVICE	NUMBER OF PREGNANCIES	TOTAL NUMBER OF PREGNANCIES WASTED	PREGNANCY WASTAGE RATE PER 1,000 PREGNANCIES
Total	2,314	275	118.8
City and ward	895	130	145.3
Semiprivate	775	72	92.9
Private	644	73	113.4
Private and semiprivate	1,419	145	102.2

TABLE VII. INFANT MORTALITY RATES ACCORDING TO ECONOMIC STATUS

TYPE OF SERVICE	NUMBER OF LIVE BIRTHS	NUMBER OF INFANT DEATHS	INFANT MORTALITY RATE PER 1,000 LIVE BIRTHS
Total	2,012	122	60.6
City and ward	740	70	94.6
Semiprivate	703	20	28.4
Private	569	32	56.2
Private and semiprivate	1,272	52	40.9

TABLE VIII. INFANT SURVIVAL RATES ACCORDING TO ECONOMIC STATUS

TYPE OF SERVICE	NUMBER OF PREGNANCIES	NUMBER OF SURVIVING INFANTS	NUMBER OF SURVIVING INFANTS PER 1,000 PREGNANCIES
Total	2,285	1,890	827.1
City and ward	868*	670	771.9
Semiprivate	775	683	881.3
Private	642*	537	836.4
Private and semiprivate	1,417	1,220	861.0

*The results of the last pregnancy for 27 of the city and ward group and 2 of the private group were unknown.

The combined effect of pregnancy wastage and infant mortality is brought out in Table VIII which shows the number of infants surviving the first year of life per 1,000 pregnancies. A thousand pregnancies in the service group produced 772 infants one year old, while 1,000 pregnancies in the self-sustaining group produced 861 surviving infants.

Although pregnancy wastage and infant mortality counteract increased fertility and tend to stabilize the size of the family, they are in themselves costly processes. Abortion alone is an enormous problem.[4]

SUMMARY AND CONCLUSIONS

1. Fertility rates for 964 women have been analyzed.

2. There is an inverse relationship between size of family and economic status.

3. The average interval between delivery and succeeding pregnancy for the group supported by public funds was 12.5 months while the interval for the self-sustaining group was 22.4 months.

4. Reproductive wastage (abortions, miscarriages, and stillbirths) and infant mortality are highest in the low-income group in which fertility is greatest.

5. One thousand pregnancies in the group supported by public funds produced 772 infants one year old while 1,000 pregnancies in the self-sustaining group produced 861 surviving infants.

6. Greater reproductive wastage and a higher infant mortality rate partially compensate for the increased incidence of reproduction in the low income group.

The author is indebted to Jacob Yerushalmy, Ph.D., Albany, New York, for his analysis of the statistics presented in this paper.

REFERENCES

(1) *Pearl, R.:* Lancet **225**: 607, 1933. (2) *Sydenstricker, E.:* Pub. Health Rep. **44**: 2101, 1929. (3) *Pearl, R.:* Human Biol. **4**: 525, 1932. (4) *Taussig, F. J.:* Am. J. Obst. & Gynec. **22**: 729, 1931.

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Defendi, Stefano: The Amino-Acid Curve in the Blood of Women with Tumors of the Uterus and of the Ovary, Folia gynaec. **25**: 392, 1938.

The author studied the function of the liver in 44 patients with tumors of the uterus or ovary in women who had no evident functional liver alteration. The amino acid curve of Bufano was employed, which, in his opinion, is a most sensitive test for the determination of the deaminization power of the liver. Studies were made prior to operation and on the second, fifth, and ninth days postoperative. In 75 per cent of the cases a slight hepatic alteration was found. During the first forty-eight hours postoperative, there is an alteration of the amino acid curve, which is diminished in five days and returns, almost always, to normal in nine days. The manifestations, which are not very severe and transitory, were found to be directly proportionate to the severity of the operative procedure and the type of anesthesia employed. More profound changes were found when cloro-ether was used and less with novocaine.

Mario A. Castallo.

VITAMIN A DEFICIENCIES IN PREGNANCY*

With Case Reports On Two Unusually Severe Examples

Wilbur A. Ricketts, M.D., F.A.C.S., Dayton, Ohio

EXPERIMENTS have indicated that while pregnancy is a normal physiologic process, it makes additional demands on the maternal organism from the standpoint of nutrition. These experiments have indicated, for instance, that a vitamin A intake adequate under other conditions may fail to meet the increased requirements during pregnancy.

Garry and Stiven[1] point out that both lactation and pregnancy thus may be considered effciency tests and that dietary deficiencies in a population are more likely to manifest themselves more clearly in pregnant and nursing women than in the general adult population.

Jeans and Zentmire,[2] Jeghers,[3] Park,[4] and Youmans and Corlette[5] have reported on the new instrument and technique which give data in relation to the vitamin A status of the subject tested.

Jeghers[3] has also shown correlation between this test† when the vitamin A content of the diet was very much reduced. During this experiment the dark adaptation curve was progressively impaired until subjective night blindness was produced.

The observations of Maxwell,[6] Green,[7, 8] and Moore[9] suggest the importance of an adequate intake of vitamin A during pregnancy.

While several reports have appeared in connection with the biophotometer tests of children, medical students, and other medical surveys, none of the reports has been in relation to the vitamin A status by means of this clinical test during pregnancy.

The biophotometer tests herein reported‡ were made using the regular technique as described by Jeans[2] and others, but in a few instances the test was shortened to thirteen minutes, obtaining the first light threshold which is obtained twenty seconds after the bleaching light is turned off. While this reading does not give the complete dark adaptation curve, experience has shown that it is useful in selecting the most severe cases. The complete curve was made on all severe cases reported.

The cases reported are all private patients, financially able to secure all the needed food and care. They included dietitians, nurses, and other professional women. Several were the wives of physicians or dentists. The average age of the group was 29 years, ranging from 20 to 49 years.

Jeans[2] has suggested that a reading of 0.6 millifoot candles twenty seconds after the bleaching light is turned out, be used as a dividing line between the normal and borderline cases. Youmans and Corlette[5] suggest 0.7 millifoot candles for adults. Jeghers did not attempt to set any particular limit, but divided the medical students in his survey into three groups.

*Presented in part before the Clinical Conference, Miami Valley Hospital, Oct. 22, 1937.

†Biophotometer.

‡These tests were made through the cooperation of Dr. Ira O. Park of Dayton.

For the purpose of roughly dividing this small series into groups, those ranging from 1 millifoot candle were classed as good, between 2 and 1 millifoot candles, as fair, between 3 and 2 millifoot candles as poor, and below 3 millifoot candles as very poor. Of the 40 individuals tested by this method of classification, 16 were classed as good, 17 fair, 3 poor, and 4 very poor. There was an opportunity of rechecking 19 cases after taking vitamin A or carotene in oil. All showed an improvement as indicated by the test. The most spectacular improvement was shown in the poor and very poor cases who were given from 60,000 to 90,000 units of carotene in oil per day until they gave a response that might be classed good by the biophotometer test. These cases also improved clinically, and the amount of carotene in oil given was reduced to 30,000 units per day after the maximum improvement had been reached. While all these 19 cases improved, some seemed especially more responsive to carotene in oil. It was also observed that in the early months of pregnancy, most of the patients taking small doses of the vitamin A concentrate and having readings in the "fair" group, responded to larger doses of vitamin A concentrate and those re-checked improved their biophotometer tests to that classified as "good."

CASE HISTORIES

CASE 1.—(No. 104.) Mrs. J. F. P., white, aged 20 years, gravida ii. As a child, the patient ate irregularly and had frequent colds. From history it appears that the patient was more or less vitamin A deficient for the greater part of her childhood and markedly so during the years preceding this pregnancy. Patient was first pregnant at 16 years of age (1934) with an abortion due to accidental fall. There were no complications. In 1934 she had a tubal infection treated by the Elliot short wave; also an appendectomy and suspension of uterus in latter part of 1934; in 1935, pyelitis. Last menstruation, Dec. 14, 1936; delivered Sept. 25, 1937. On Feb. 5, 1937, she was admitted to the hospital with vomiting and hemorrhage; she continued to vomit until March 26, 1937, when she presented the following symptoms: Night-blindness; inability to stand even normal daylight (wore dark glasses and kept shades down); constant severe headache; constant vomiting—nothing tolerated; hair dry, coarse, and brittle; skin dry and scaly; eyes, cornea dull and lusterless; extreme weakness; and mild anemia.

Patient was referred for x-ray of sinuses with a negative report. The usual ophthalmologic examination revealed nothing to account for her symptoms. The patient was then referred for a biophotometer test. Her initial test on March 26, 1937 showed a low threshold and aptation test (Fig. 1). After three minutes' light exposure, 5.2 millifoot candles were required for her to detect the test spot.

Following the test the patient was given 60,000 units of carotene in oil for three days; then increasing to 90,000 units, decreasing the dose as improvement was shown on the biophotometer as given below:

BIOPHOTOMETER TESTS

March 26, 1937—5.2 millifoot candles of light
April 6, 1937—1.80 millifoot candles of light
April 26, 1937—0.52 millifoot candles of light
June 7, 1937—0.260 millifoot candles of light
July 10, 1937—0.380 millifoot candles of light
Oct. 6, 1937—0.69 millifoot candles of light after delivery

This patient improved in every way following the addition of carotene in oil to a balanced diet. Headache, night blindness, and photophobia disappeared in one month, and the patient resumed all usual activities. Patient weighed 114 pounds on March 26, 1937, and on Sept. 24, 1937 had gained 20 pounds. Delivery was normal, patient had ample lactation, and felt fine.

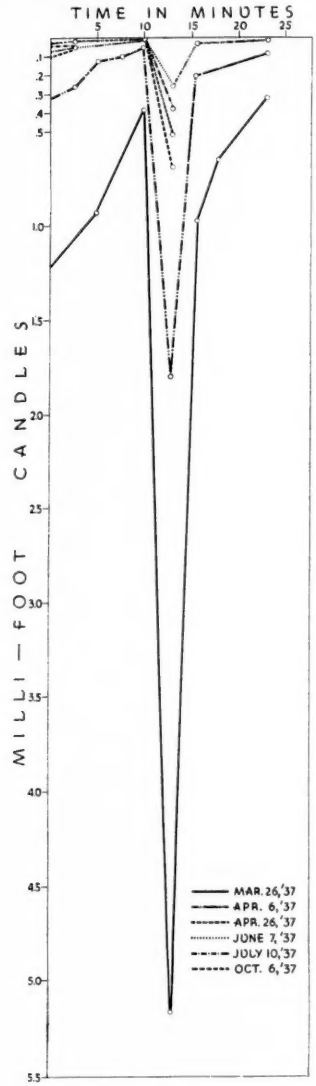

Fig. 1.

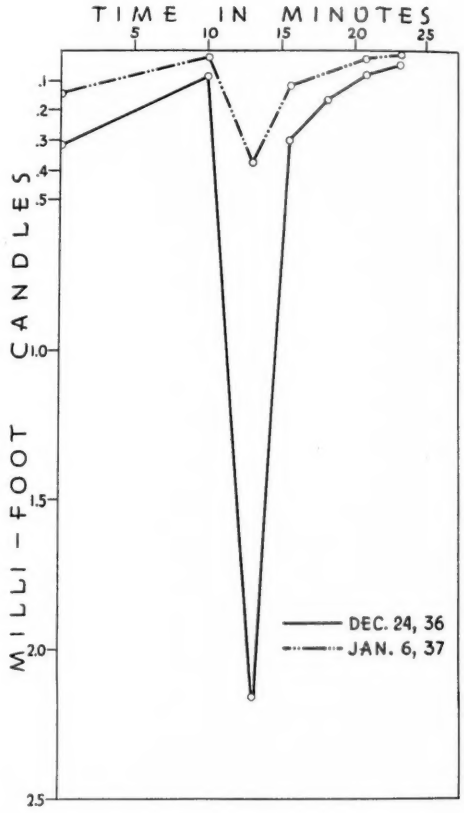

Fig. 2.

Fig. 1.—Biophotometer test curves on Case 1.

Fig. 2.—Biophotometer test curves before (lower curve) and after (upper curve) carotene in oil therapy of uncomplicated vitamin A deficiency during pregnancy.

CASE 2.—(No. 87.) Mrs. E. O., aged 20 years, white. Last menstruation Dec. 15, 1936. As a child had pneumonia. Mother reports she was the only child and had always been a problem due to dietary irregularities. Patient worked in a downtown department store as a clerk until May 10, 1937. At that time she came to the office with the following symptoms: Marked light sensitiveness, exhaustion, nausea and vomiting, blurring of vision and night blindness, clouded mentality, and headache.

The patient was referred for biophotometric examination with the following results (Fig. 2):

May 10, 1937—4.4 millifoot candles
June 20, 1937—1.80 millifoot candles
August 1, 1937—0.59 millifoot candles
Oct. 1, 1937—2.40 millifoot candles after delivery

After the initial test, the patient was first given 60,000 units of carotene in oil, increasing to 90,000 for several days until improvement was shown on the biophotometer reading; then the amount was reduced. On Aug. 1, 1937, the patient was rechecked by the photometer with a high normal reading. She felt better than she had ever felt. At this time the patient, who was never very cooperative, stopped taking carotene and took no more before she was delivered Sept. 19, 1937.

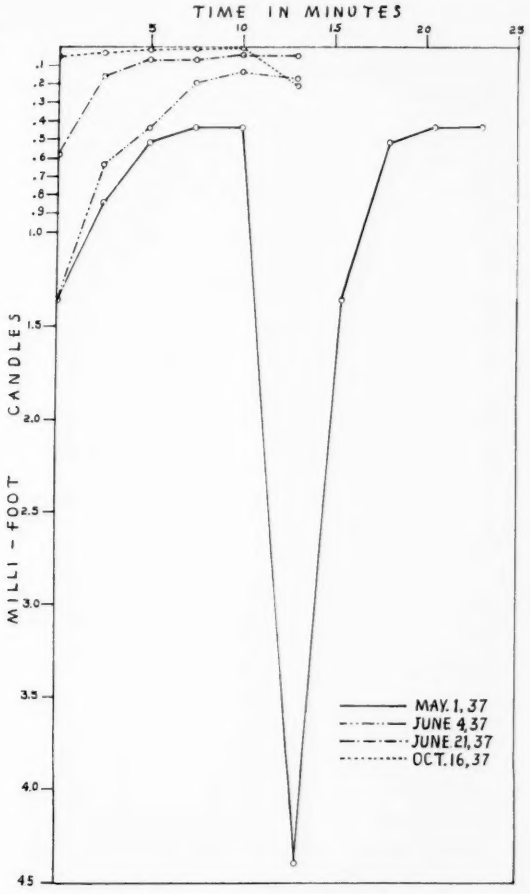

Fig. 3.—Biophotometer test curves on Case 2.

Following delivery, the patient was rechecked with the biophotometer and was again low. She presented the following symptoms at this time: Tiring easily, marked nervousness, weakness, and insufficient lactation.

Lack of cooperation on the part of this patient shows her in marked contrast to the other patient. She did not continue her vitamin regime long enough to supply a reserve. She in no way followed instructions.

These two cases present the severe type of vitamin A deficiency, in which, unless prompt action had been taken the patients would probably have died and been classed as toxemia of pregnancy, and these illustrate the importance of the careful checking of all pregnancies for vitamin A deficiencies as early as possible.

Here we have two young women of the same age; both gave histories suggestive of prolonged vitamin A deficiencies; then with the beginning of pregnancy with the added nausea and vomiting, we find all conditions necessary to the production of a severe deficiency.

The second of these cases, as compared to the first, illustrated the importance of the continuation of an assured vitamin supply up to delivery.

SUMMARY

1. Severe deficiencies in vitamin A simulate so-called toxemias of pregnancy.

2. Women in the better class (financially) are often low in vitamin A during pregnancy, due to method of living and demands on their strength.

3. Administration of carotene in oil in severe deficiencies brought spectacular response.

4. Early check of all pregnancies with the biophotometer is important.

REFERENCES

(1) *Garry, E. C., and Stiven, D.:* Nutrition Abstr. & Rev. **5**: 855, 1935. (2) *Jeans, P. C., and Zentmire, Zelma:* J. A. M. A. **102**: 892, 1934. (3) *Jeghers, Harold:* J. A. M. A. **109**: 756, 1937. (4) *Park, Ira:* (To be published.) (5) *Corlette, M. B., Youmans, J. B., Frank, Helen, and Corlette, M. G.:* Am. J. M. Sc. **195**: 54, 1938. (6) *Maxwell, J. P.:* Proc. Roy. Soc. Med. **23**: 639, 1929. (7) *Green, H. N.:* Lancet **223**: 723, 1932. (8) *Idem:* Proc. Roy. Soc. Med. **28**: 1400, 1935. (9) *Moore, T.:* Lancet **223**: 669, 1932.

Eichner, E.: Value of Knee-Chest Exercises in Postpartum Retrodisplacement. Ohio State M. J. **33**: 1233, 1937.

The study comprised 316 women having 402 deliveries in the obstetric service at Mount Sinai Hospital; 22.7 per cent of the uteri of 211 patients instructed in knee-chest exercises during their stay at the hospital were found in a posterior position at their first dispensary examination, while 27.7 per cent of the uteri of the 191 patients not so instructed were retroplaced at their first post-partum examination. In the entire series 101 patients, or 25.1 per cent of the total, had retrodisplacements at their initial post-partum visit. The percentage of posterior displacements increased with the parity from 20 in the primiparas to 41.2 in the quintiparas; 30.4 per cent of the posterior displacements treated by knee-chest exercises were failures and, of these, 6 patients responded to the use of a pessary and 7 were discharged. In cases in which the pessary failed, the knee-chest position also failed. In twelve patients the uterus became anterior without treatment for the retrodisplacement in an interval less than that required for either pessaries or knee-chest exercises. The conclusion is that knee-chest exercises are valueless in the treatment of post-partum retrodisplacement except during the third and fourth weeks of the puerperium, when these exercises appear to reduce the percentage of displacements.

J. P. GREENHILL.

THE CHANGES OF THE URINARY TRACT ASSOCIATED WITH PROLAPSE OF THE UTERUS

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IN RECENT years numerous articles have been published regarding the surgical treatment of uterine prolapse. Most of these have stressed the advantages, techniques, and results of the various types of surgical procedures recommended by the individual authors. Vaginal hysterectomy, obliteration of the vagina, interposition of the uterine body, and, more recently, the Manchester type of parametrial fixation are operations of choice. The authors of these various articles have failed generally to stress the complications of neglected uterine prolapse. The changes that occur in the urinary tract in women who have suffered for a long time from prolapse of the uterus should be reemphasized, particularly the obstruction of the lower urinary tract with resulting hydroureter, hydronephrosis, pyonephrosis, and renal insufficiency.

Three particular reasons have prompted the following investigation. First of all, the average patient, when asked why she did not have the prolapse repaired, occasionally replies that "she had received medical advice that the condition would never kill her and, if it did not interfere with her activities, to neglect it." The cases that I wish to report will show that this is an erroneous statement. Second, the post-mortem study of a woman who had had complete prolapse of the uterus for twenty years (Case 6) suggested that the bilateral pyoureters and pyonephrosis which were found had resulted from the slinglike structure of the uterine arteries as they were pulled over the ureters. Third, since surgery is being employed possibly more frequently than in the past, some justification for its continued practice seems necessary.

The obstruction of the urinary tract in procidentia is not a new observation. In 1846 Virchow described the changes in the urinary tract with marked prolapse of the uterus. Halban and Tandler expressed the opinion, from a study of their autopsy findings, that the dilatation of the ureters was due to the compression outside the bladder. Brettauer and Rubin reported that frequent secondary findings in cases of neglected prolapse of the bladder were pyoureter and pyonephrosis.

The three theories frequently offered for the mechanical obstruction of the passage of the urine from the kidneys through the ureters, bladder, and the urethra in cases of prolapse of the uterus are as follows:

1. Kinking of the urethra and stasis with cystocele. If the obstruction were primarily in the urethra with strangulation, you would expect frequently to find a large amount of residual urine. From our observation this is not true.

2. The intramural stretching of the ureters in the bladder wall with stenosis. If the intramural stretching in the bladder wall were the primary reason, you would naturally expect the dilatation of the ureters to occur from that point. This has not always been shown.

3. Compression of the ureters outside the bladder. Concerning this theory, regarding the compression of the ureters outside the bladder, Brettauer and Rubin feel that if the bladder were a solid structure compression of the ureters as they were drawn through the pelvic outlet would be possible, but, since the bladder itself is compressible and not solid, they believe that the ureters could not be sufficiently compressed. However, it is an established fact that obstruction of the upper urinary tract can result from certain anatomical arrangements of blood vessels, as when there is an aberrant renal artery running to the lower pole of the kidney. Upon release of this obstruction, the dilatation of the upper ureter disappears. The anatomic relationship of the lower end of the ureter and the uterine artery shows that the ureter passes under the uterine artery to reach the bladder. As the uterus is prolapsed more and more through the pelvic outlet, the uterine arteries become slings over the ureters and, if this condition persists, the ureter becomes partially obstructed and the secondary changes above the obstruction progress. The changes of hydroureter followed by pyelitis and pyonephrosis and, finally, renal insufficiency are similar to the changes that occur in prostatic obstruction in the male, or, as a matter of fact, any lower urinary obstruction.

Together with the autopsy findings of Case 6, I am also reporting five additional cases of prolapse of the uterus and bladder in which x-rays showed urinary changes. In order to obtain the data regarding the urinary systems in these patients, the following procedures were used:

Besides a complete physical examination and a thorough history, a routine urinalysis was performed. Nonprotein nitrogen, creatinine, and sugar determinations were made on the blood. A phthalein function test was done on the kidneys. X-rays of the urinary tract were taken, using intravenous neo-iopax. The pyelograms were taken with the patient standing and also lying down. The same determinations were made after operation when the patient returned for check-up.

CASE 1.—Mrs. E. H. (Hospital No. 18308). This 54-year-old, white female entered the hospital complaining of something falling out of her. As far as she knew this had been going on for about four years. About three weeks before admission, while standing, the uterus prolapsed about four or five inches. Heretofore, it had only presented at the vulva. At the present time she is only nine years past the menopause, has had two children, and, according to her story, had no difficulty with her deliveries. General physical examination, other than the prolapse, revealed a blood pressure of 195/100. Urinalysis was entirely negative. Phenolsulphonephthalein test was 78 per cent in two hours; blood Wassermann test, negative; blood nonprotein nitrogen, 39.2; blood sugar, 114.2 mg.; creatinine, 1.28. She was operated upon two days after admission. The Manchester type of vaginal repair was performed. She made a normal convalescence and was discharged in good condition.

CASE 2.—Mrs. S. H. (Hospital No. 15580). This 37-year-old woman stated that for the past year she had had "falling of the womb." She had been married eleven years and had three children. The first labor was very prolonged and delivery was by means of instruments. Her menstrual flow had been normal for the past four or five months. She had been unable to keep her uterus in the pelvis—it presenting outside the vulva at all times.

On physical examination there was nothing very abnormal except the prolapse of the uterus. Her urine on two occasions contained a slight amount of albumin. There were no casts. The blood pressure was 180/95; blood nonprotein nitrogen, 37.6 mg.; sugar, 94.7; creatinine, 1.24; phenolsulphonephthalein test, 50 per cent in two hours. Because of the marked ulceration of the prolapsed uterus and vagina, it was decided to hold the uterus temporarily in place by fixing it to the anterior abdominal wall. This was done under ether anesthesia. The patient was discharged to return for further repair.

CASE 3.—Mrs. L. W. (Hospital No. 22116). This 59-year-old housewife had had a sense of lack of support for the last two years, and for the last six weeks had complained of a tumor coming from the vagina. She also complained of burning and frequency of urination. There was no incontinence of urine. Blood pressure was 150/92. Urinalysis showed a trace of albumin and an occasional white blood cell. Examination of her blood showed a nonprotein nitrogen of 29 mg. per cent, creatinine 1.1 mg. per cent, sugar 100 mg. per cent.

After two weeks' hospitalization she was operated upon. A vaginal hysterectomy and posterior repair were performed under ether anesthesia. She was discharged three weeks after operation in good condition.

CASE 4.—Mrs. E. B. (Hospital No. 18645.) This 48-year-old patient stated that she had never been pregnant and, for the last twenty years, had had something protruding through the vagina. The condition progressed, until eight years ago when the patient could not keep the uterus inside her without wearing some type of support. For the past six months she had been unable to replace the uterus. She also complained of frequency of urination and constipation. Urinalysis was entirely negative. Blood pressure was 150/80. Because of the edema and ulceration of the prolapsed uterus, it was replaced and held in place by a Menge pessary, and the patient was advised to return home. At that time blood examination showed nonprotein nitrogen 42.4, sugar 118.3, creatinine 1.4, phenolsulphonephthalein test 85 per cent in two hours. She returned about six weeks later. The pessary was removed and a vaginal hysterectomy was performed. Her convalescence was uneventful except for a cystitis which developed two weeks after operation. Catheter specimen of urine showed many pus cells, and *Streptococcus viridans* was isolated.

CASE 5.—Mrs. B. O. (Hospital No. 19013.) This 72-year-old woman, mother of five children, stated that the first sensation of bearing-down discomfort in her pelvis was observed twelve years ago. It did not bother her a great deal until two years ago when she fell down and injured her knee cap. When she got up and around after six weeks in bed, she noticed that something protruded from the vagina. This had become progressively worse until she sought consultation. Blood pressure 180/95. Urine showed many white blood cells, otherwise negative. Blood chemistry: nonprotein nitrogen 35.2, sugar 39.7, creatinine 1.2; phenolsulphonephthalein test 75 per cent in two hours.

After several days' preparation in the hospital, a Manchester type of operation was performed. Her convalescence was uneventful, and she was discharged in good condition.

CASE 6.—Mrs. I. G., aged 66 (Hospital No. 12299). For the past six years this woman had had a prolapse of the uterus, which produced no more symptoms than a dragging down feeling and general inconvenience. During this time she lost 81 pounds, but had continued to do her usual housework. For three weeks her bearing-down pain had been severe and she was prevailed upon by her friends to seek medical attention.

Thirty-three years ago her only pregnancy terminated in a difficult instrumental delivery of a stillborn child.

Physical examination was of a dehydrated emaciated woman, very alert. Except for moderate thickening of the peripheral blood vessels, the only other finding was a complete uterine prolapse. Her urine was strongly positive for albumin and the sediment showed many pus cells. She had a moderate secondary anemia and her white blood cells were elevated to 18,000. Blood sugar was 158.8 mg. per cent; blood nitrogen, 120 mg. per cent; creatinine was correspondingly elevated to 3.4 mg. per cent; and the chlorides were normal. Carbon dioxide combining power was 15.5.

The obvious dehydration was combated with intravenous glucose and subpectoral saline daily, so that by the third day her nonnitrogen had dropped to 109.6 mg. per cent and creatinine to 3.38 mg. per cent, and her carbon dioxide combining power rose to 26 per cent.

Efforts were renewed in the direction of forcing fluids by means of a continuous intravenous drip. Though her sensorium remained absolutely clear, she began to show signs of uremia with occasional twitchings and generalized shaking, not true convulsions. She continued to be nauseated constantly and to vomit at very frequent intervals. On the tenth day she had a very definite sudden convulsive seizure and died.

POST-MORTEM FINDINGS

Gross Examination.—The body was that of a fairly well-developed but thin elderly white woman, 151.25 cm. (60.5 inches) in length, and 66 years of age. Rigor mortis had not yet developed and there was only slight post-mortem lividity of the dependent portions. There was no edema of the face or extremities. The hair was gray and abundant. The ears and nasal passages were negative. The eyes were blue-gray, the pupils being round, equal and regular. The upper and lower teeth were replaced by false plates. The neck was thin. The chest was symmetrical. The breasts were small and grossly normal. The abdomen was flat and soft. There were venepuncture wounds and ecchymosis in both antecubital fossae. Just above the internal malleolus of the right ankle was a short incision 2 cm. in length through which intravenous glucose had been administered.

There was complete eversion of the vagina due to extreme prolapse of the uterus. The cervix of this organ presented at the most dependent portion and exhibited one large and several small superficial erosions. The entire mass was inflamed and exuded a foul odor.

Peritoneal Cavity.—The body was opened with the usual Y-shaped incision. The subcutaneous tissues were moderately moist. The omentum which was thin was stretched over the abdominal organs and was adherent to the abdominal walls just below the brim of the pelvis. On reflecting this, approximately 400 c.c. of turbid reddish yellow fluid were found free in the pelvic cavity and also about the various viscera. The serosal surface of the cecum was dark purplish red and covered with adhesions. In attempting to free the cecum and ascending colon, it was found that they formed part of a large adherent inflammatory mass which also included the right kidney and ureter and a considerable amount of perirenal fat. A similar large adherent mass was found on the left side of the abdomen. These will be described in more detail later.

In the pelvis only the fundus of the uterus was seen. It was present in a depression in the pelvic floor through which the body of the organ had prolapsed. The Fallopian tubes were stretched due to the tension of the prolapsed uterus.

Adrenals.—These glands were essentially negative.

Kidneys.—The entire genitourinary tract was removed en masse and then carefully dissected. Both kidneys were surrounded by a large amount of fat which, as it was removed, was seen to be infiltrated with a thin, reddish gray, foul-smelling, inflammatory fluid. As the fat immediately around the kidneys was removed the fluid became definitely purulent. Both organs were soft, large, and contained many thin-walled, fluctuant, cystic cavities. In stripping a piece of capsule from the surface of the left kidney, the underlying cortex was so thin and cystlike that the tissue ruptured and permitted considerable dark brown, foul-smelling, purulent material to escape.

Before continuing with the examination of the kidneys, a probe was inserted into the urethra and this structure was opened to the bladder. The bladder was contracted and did not contain any urine. Its wall was thickened. The mucosa was grayish brown and necrotic and was thrown into deep folds which were covered with the same sort of fluid purulent material that was contained in the left kidney.

Both ureters were markedly distended, thickened, and appeared dark purplish red in color. They were 2 cm. in diameter, and there was evidence of constriction in them about 3.5 cm. from the bladder where the uterine arteries cross, as shown in Fig. 1. On opening the left ureter at its entrance into the bladder a large amount of the same gray, foul-smelling, purulent fluid poured from it. The entire

length of the ureter was opened. The mucosa was considerably thickened, appeared to be focally necrotic and was soft and greenish gray.

The left kidney was then incised longitudinally. The pelvis was distended and filled with the same sort of material as found elsewhere. The parenchyma was almost entirely replaced by large and small cysts. In a few places there were remnants of cortical pyramids extending inward between the cysts.

The right kidney and ureter were not opened at this examination. Grossly they resembled in all respects the left organs and a museum specimen will be made from the entire genitourinary system to show one kidney and ureter intact while the other organs will disclose the deeper changes.

Fig. 1.

Genitalia.—The prolapsed uterus was small and atrophic. There was a small leiomyoma in the wall of the fundus. The Fallopian tubes and ovaries were also atrophic. The fimbriated extremity of the left tube was stretched over a parovarian cyst, measuring 3 by 2 cm. On the anterior surface of the everted vagina, there was a fairly large area of hyperkeratinization of the mucosa measuring 3 cm. in diameter. On the posterior surface there were several much smaller similar lesions.

CONCLUSIONS

1. In neglected cases of uterine prolapse, changes in the urinary tract may result.

2. These changes, hydroureter, hydronephrosis and, eventually, renal insufficiency, are probably caused by obstruction of the lower end of the ureter by the slinglike position of the uterine artery as it is pulled over the ureter.

3. Replacement of the uterus by pessary or operation relieves the obstruction.

4. Complete histories and laboratory findings in five cases of prolapse of the uterus and post-mortem findings in one other case are reported.

The author desires to thank Dr. John A. Sampson for advice and permission to include certain cases.

REFERENCES

Virchow, R.: Gesammelte Abhandlungen, Frankfurt am Main, 1856. *Halban, J., and Tandler, J.:* Anatomie und Aetiologie der Genitalprolapse beim Weibe, 1907. *Brettauer, J., and Rubin, I. C.:* Am. J. Obst. & Gynec. **6**: 696, 1923.

A STUDY OF A CAUSE OF HYDRAMNIOS

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ONE of the causes of hydramnios and of its commonly associated fetal lesions, is infection.

In 1931, Goodall published a paper entitled "Hydramnios, a Theory and a Discussion,"[1] in which it was advanced that hydramnios, in most cases, is the result of an infective inflammatory hypersecretion of the amnion, and that the defections in the fetus also depended upon that same agency. It was also pointed out that in cases of hydramnios one is always cautious as to the prognosis of the fetus, owing to the frequency of fetal defects. A study of these defects made it very clear that in cases of hydramnios, the fetal anomalies were always the same. They fell into distinct categories: (1) A normal child; (2) external deformities, such as synechias or amputations due to inflammatory adhesions or bands; (3) hydrocephaly; (4) spina bifida with meningocele; and (5) anencephaly. It was pointed out that the uniformity of these fetal defects associated with hydramnios, argued a common causal agency and that amnionitis answered the problems. Inflammation of the amniotic sac could account for the hypersecretion of fluid, for the synechiae, for the adhesions and amputations, and it was pointed out that the intensity of this inflammation would determine whether there would be merely hypersecretion, or whether there could also be fusions of contiguous parts and amputations of limbs. It was also argued that the result of amniotic infection upon the fetal nervous system would depend upon the time of the amniotic invasion in relation to the stage

of fetal development. The neural canal of the fetus is developed from the fetal ectoderm, which is continuous with the amnion. So, if infection got into the amniotic sac after the fetal spinal cord had already closed, the child's nervous mechanism would not suffer, and external adhesions at that later date, when fetal movements had probably already developed, would be almost impossible. Therefore, in cases of late hydramnios, normal babies would be the rule. If, on the other hand, the amniotic infection developed just before the cord closed at its latest closing parts, that is, the cervical and lumbar regions, then spinal closure would be completed before hypersecretion of the brain ependyma and cord membranes had developed, and hydrocephaly would be expected to develop later. If, again, the amniotic infection developed at an earlier date, before the spinal closure, hypersecretion would set in, and internal spinal pressure would prevent closure and spina bifida would consequently develop. And last, if the amniotic infection got into the nervous system in the early stages of the neural development, normal growth would be inhibited and the consequence would be an anencephalic monster. It may be emphasized here that an examination of the fetus of abortions frequently reveals acute infective processes in the amnion, and exudate in the crevices of contiguous fetal parts. Such acute infections frequently associated with preabortal maternal fever invariably result in death of the fetus and a casting off of the products of conception. In the less acute cases, where the infection inclines more to the exudative than to the hypersecretive types, especially before fetal movements have begun, synechias and adhesions will be the dominant defects. Whereas, in the lowest types of infection, the common types, hyperfunction, that is, hydramnios, will be the dominant sign. These types of infection, when access to the fetal nervous and other systems is obtained, lead to changes variable in degree and extent. In the milder forms this condition may remain local in the ventricles of the fetal brain. In the more acute cases, the infection may spread by the blood stream to other systems.

That this explanation is probably correct is shown by the following cases:

Case 1.—A primipara, 38 years of age, weight 88 pounds, 5 feet in height, consulted Goodall. She had a justominor pelvis, and it was decided to perform a cesarean section at full term if there was any disproportion. She was examined three weeks before full term. There was a definite, but mild, degree of hydramnios, and it was quite impossible to make out the presentation. An x-ray was taken, which showed a breech with an enormous hydrocephaly, which filled the whole subdiaphragmatic area. A cesarean section was done, and after delivery of the body, the aftercoming head was so enormous that the posterior fontanel was punctured to facilitate extraction. Fully a quart of fluid escaped from the ventricles. Examination of the body revealed a fusion of three fingers which were nearly amputated by a tough thready adhesion which had an attachment to the amniotic wall, but which was broken on delivery, and a tag 2 inches long pendent from the constricted fingers. The little finger of the other hand had been cleanly amputated by an adhesion. Two toes of one foot were fused and almost amputated by a thready adhesion, and two toes of the other foot were cleanly amputated, the attachment of which outside the big toe was still plainly visible (Fig. 1). It was at once hypothecated that if an infection of this severity had caused these deformities and had entered the central

nervous system of the child before closure of the neural canal, it might be possible to demonstrate infective processes in the other organs of the body, and most likely these would be found in the heart, the only organ operating at normal capacity at that time. Accordingly, a careful autopsy was performed. No gross lesions were found, except two pericardial milk spots on the posterior wall. Numerous blocks were taken from all the organs, and these were carefully mounted.

The sections of the cerebral ventricular lining showed signs of blocking of the lymph spaces by lymphocytes, and thrombosis of a few of the smaller blood vessels (Fig. 2). But in the heart there were all the signs of a well-defined infection of the adventitia at one side of the coronary arteries, and an infiltration of the contiguous muscularis of the artery in about one-fourth of its circumference, and internal to

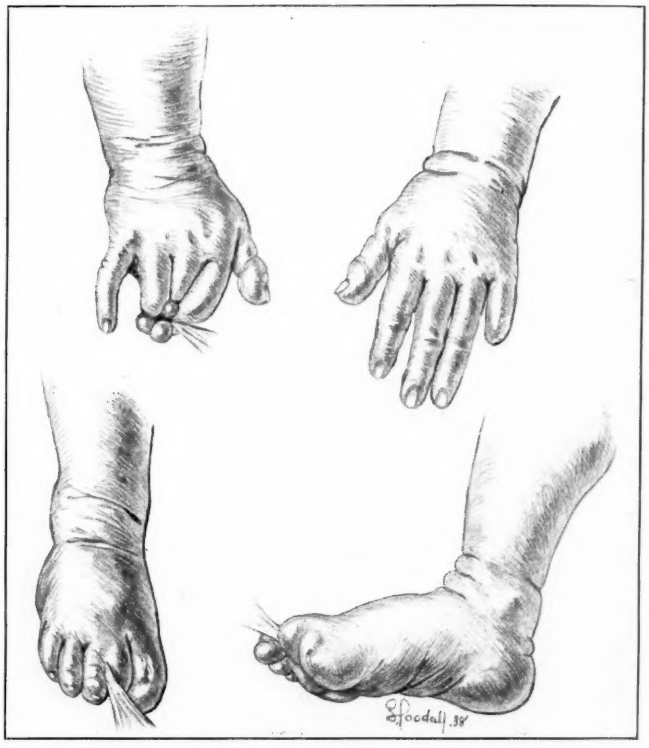

Fig. 1.—Showing amputated and deformed digits.

this, a clear-cut endarteritis, involving one-third of the arterial caliber, lifting the intima off its bed, but leaving the other two-thirds of the intima intact (Fig. 3). The dominant leucocytic infiltration was eosinophilic. There was thickening of the pericardium at two spots. The parent's Wassermanns were negative; there was no evidence of infection elsewhere. On questioning, the patient stated that she was seized with a subacute tenacious cold just about the time she became pregnant. It is thought that one or more of her sinuses were probably involved, judging from the tenacity of the infection.

The evidences point, therefore, to an infection of the amniotic sac, invasion of the spinal system and an occasional invasion of the fetal blood stream by an aberrant microbe, not a septicemia in the true sense, but the common temporary, possibly recurrent invasion. That the amniotic fluid and fetus do become infected from a primary focus in the mother is shown by the following case, reported now for the first time.

CASE 2.—A secondipara was seen by Goodall in consultation with a cardiologist. The patient had mitral stenosis with decompensation. She was then two and one-half months pregnant. Therapeutic abortion was recommended. The advice was not heeded. At the seventh month, the patient developed an acute infective endocarditis, implanted upon the chronic. High fever and chills developed. The first blood culture showed 50 colonies of *Streptococcus viridans*. A second culture, ten days

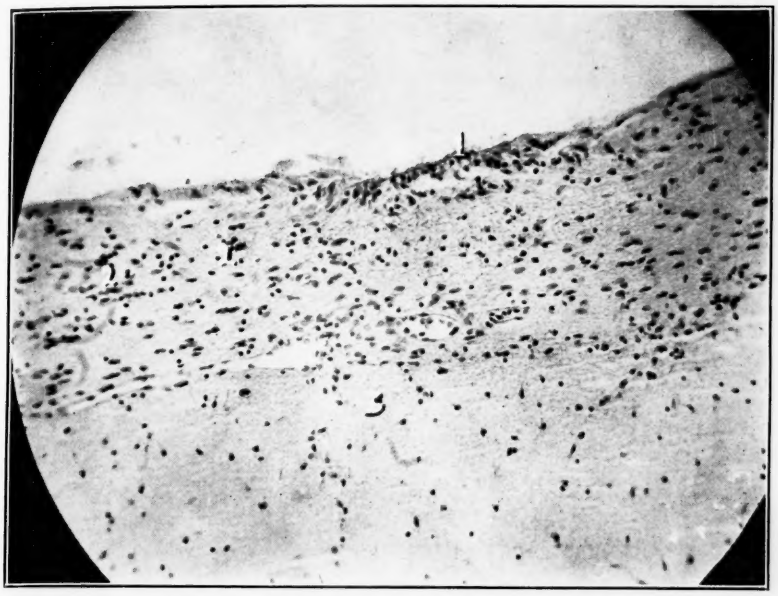

Fig. 2.—*1*, Ventricular lining; *2*, thrombosed vessels; and *3*, medulla.

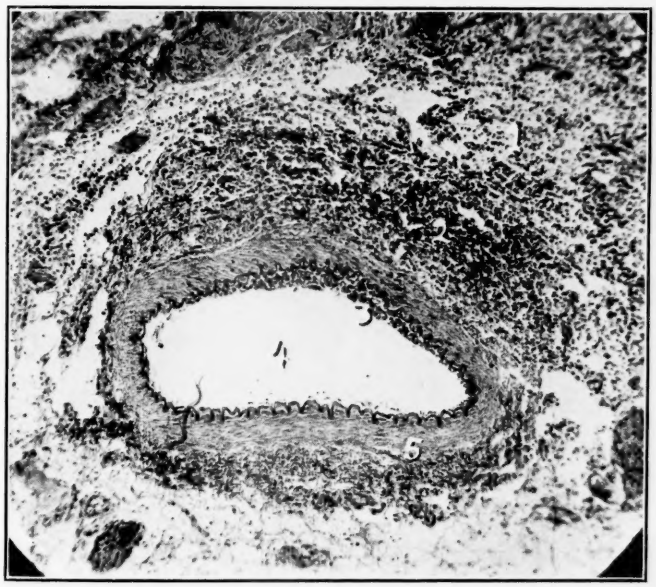

Fig. 3.—*1*, Cardiac muscle; *2*, extravascular inflammation; *3*, subintimal exudate; *4*, coronary artery; and *5*, elastica.

later, showed roughly 200 colonies. Acute hydramnios came on, and Goodall passed a small trocar through the anterior vaginal fornix, between the bladder in front and the lower uterins segment behind, for purposes of culturing the amniotic fluid. A large amount of fluid was allowed to escape slowly. After this had run some time, some of the fluid was collected as it escaped, for culture. The growth was a pure culture of the specific streptococcus. Two days later the membranes were ruptured and a living fetus was born, and cultures of its blood gave a pure growth of the same organism. The amniotic placental surface was then seared with the iron, and a small portion of placenta was cultured in medium, and gave a pure growth also. The baby died a few hours after birth. Autopsy was refused. Here we have direct evidence of invasion of the amniotic fluid, and of the fetal blood stream from the maternal cardiac focus.

COMMENT

It is not contended that all cases of hydramnios are due to infection. We do know that other causes, such as cardiac decompensation with venous stasis, will produce hydramnios, as will also congenital fetal cardiac and renal diseases, but it does seem conclusive that maternal foci of infection can, and may, transmit that infection to the amniotic sac, and if early enough may infect the fetal neural system, and may produce infectious changes in other organs. What the above related cardiac infection would have meant in a viable child, whether coronary constriction or continued infective myocardial changes would supervene, are very debatable points. However, the matter is one for theorizing, for the hydrocephaly precluded any prolonged extrauterine life in this case.

REFERENCE

(1) *Goodall, J. R.:* J. Obst. & Gynaec. Brit. Emp. **38**: 847, 1931.

CONCENTRATION OF SERUM SULFATE DURING PREGNANCY AND IN PRE-ECLAMPTIC TOXEMIA*

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THERE is probably no other condition in which the borderline between health and disease is less sharply marked than it is in the toxemias of pregnancy. Apparently, only slight alterations in physiology are necessary to convert the condition of the normal pregnant woman into one of the varying degrees of illnesses incident to one of these toxemias. Chemical analyses of the blood of patients afflicted with the toxemias of pregnancy have been significant by the absence of changes which were uniformly of diagnostic or therapeutic value. Plass has demonstrated that the concentration of the nonprotein nitrogen of such patients is within normal limits. The concentration of uric acid in the blood of the pre-eclamptic patient is increased. When the pregnant

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woman becomes edematous, there may be an increase in the concentration of plasma chlorides and a decreased concentration of the plasma proteins. In the presence of severe toxemia (eclampsia), the patient may be dehydrated and thus present a hyperazotemia.

The object of this study was to determine the concentration of serum sulfate both during normal gestation and at the time symptoms of pre-eclamptic toxemia and eclampsia developed.

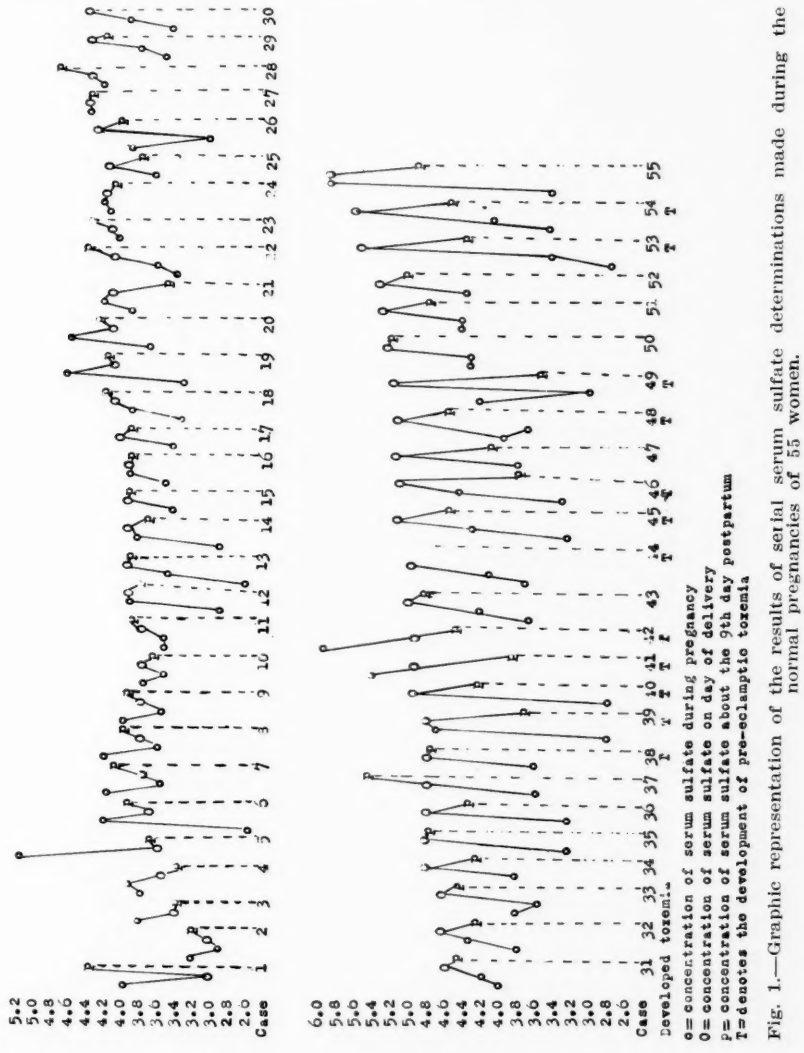

Fig. 1.—Graphic representation of the results of serial serum sulfate determinations made during the normal pregnancies of 55 women.

As shown in Fig. 1, the study was conducted according to a single plan. During the first trimester of pregnancy, if the patient appeared to be within the limits of the normal, if the urinalysis disclosed no abnormalities and if the blood pressure was within normal limits, the concentration of serum sulfate was less than 5 mg. of sulfate (1.6 mg. of sulfur) per each 100 c.c. of serum, a normal range of concentration of this substance. Less than 2 per cent of 125 nonpregnant individuals previ-

ously observed by one of us had a concentration of serum greater than 5 mg. of sulfate (1.3 mg. of sulfur) per 100 c.c. of serum. Fig. 1 shows the results of serial serum sulfate determinations made during normal pregnancies. In 16 of the 55 cases the value for sulfates was elevated 5.0 mg. per 100 c.c. of serum or more, one day post partum. In the first 39 cases represented in this table, the concentration of serum sulfate was within normal limits both at the time of delivery and again on about the ninth day post partum, with the exception of Case 37. The table shows a most interesting finding in the association of the symptoms of pre-eclamptic toxemia and the concentration of serum sulfate. Often, as indicated in the same table, in Cases 39, 40, 41, 42, 44, 45, 46, 48, 49, 53, and 54, representing those patients who had exhibited symptoms of pre-eclamptic toxemia, the concentration of serum sulfate was in the upper range of the normal or it was increased. In fact, 12 of 18 patients whose serum disclosed an abnormal increase in concentration of sulfate during

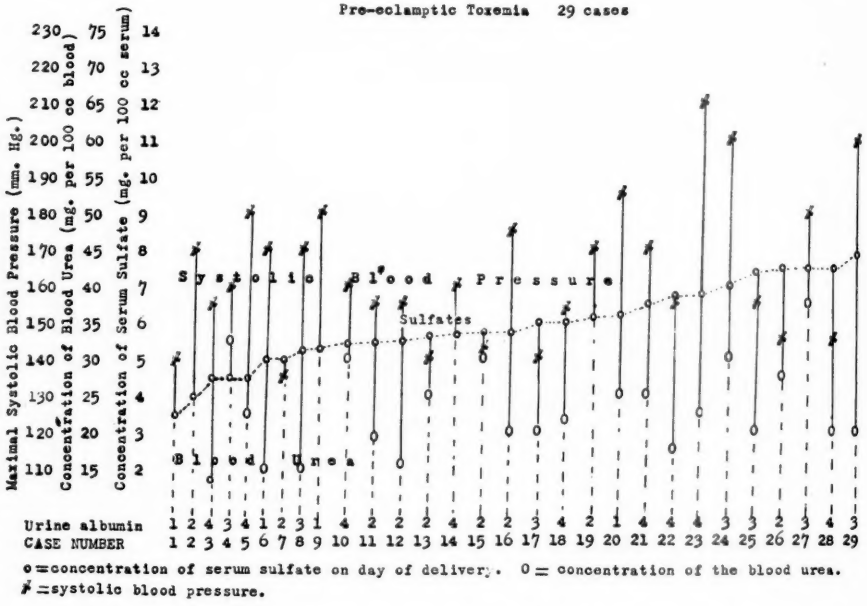

Fig. 2.—Graphic representation of the concentration of serum sulfate, the concentration of blood urea, and the systolic blood pressure at time of delivery of 29 women who suffered from pre-eclamptic toxemia.

pregnancy experienced pre-eclampsia, while none of those whose serum gave consistently normal values for sulfate throughout pregnancy suffered from toxemia. The increase in serum sulfate values antedated the appearance of toxemia in nearly all cases. However, in Cases 43, 47, 50, 51, 52, and 55 the concentration of serum sulfate was increased but the patients did not have symptoms of pre-eclampsia.

In Fig. 2, the concentration of serum sulfate, the concentration of blood urea and the systolic blood pressure at the time of delivery in 29 cases of pre-eclamptic toxemia are shown. This figure, for practical purposes, is a duplication of Fig. 1. Patients represented by Cases 1 to 7 inclusive had normal concentrations of serum sulfate although they displayed symptoms of pre-eclamptic toxemia. Patients represented by Cases 8 to 29 inclusive had both an increased concentration of serum sulfate and definite pre-eclampia.

We have observed the concentration of sulfate to be definitely increased in the serum of 6 patients who had eclampsia. In association with the toxemias of pregnancy incident to an impaired renal function,

such as glomerulonephritis, the concentration of serum sulfate may be either increased or normal, according to the status of the renal functional activity.

COMMENT

The sulfate of the serum is derived mainly from the metabolism of protein. It has been our experience that the concentration of serum sulfate is usually increased when renal insufficiency is present. It is, oddly, true that in some cases of renal sufficiency (about 10 per cent), concentration of sulfate may be increased until it is more than that which is present in the serum of a normal individual before there is an increase in the concentration of blood urea. Yet, if patients are dehydrated, as they often are in the presence of pyloric obstruction and obstruction of the urinary tract, the concentration of blood urea may be increased, while the concentration of serum sulfate remains within normal limits.

The increase in the concentration of serum sulfate in the presence of pre-eclamptic toxemias and eclampsia is a curious phenomenon. We do not believe that the increased concentration of serum sulfate plays any part in the production of, but is rather an effect of, these toxemias. Our data are not sufficient to permit formation of conclusions. Our experience, however, gained in extensive studies of the concentration of serum sulfates in both health and disease, leads us to believe that many patients having pre-eclamptic toxemia and eclampsia also have some impairment of the renal function.

If the increase in concentration of uric acid in the toxemias of pregnancy is due to hepatic faults, as Cadden and Stander have suggested, it may be that the increased concentration of inorganic serum sulfate also is related in some way to an impaired hepatic function, since the conjugation of sulfates is probably a function of the liver

REFERENCE

(1) *Cadden, J. F., and Stander, H. J.:* Am. J. Obst. & Gynec. 37: 37, 1939.

Gernez, L., and Omez, Y.: Twin Pregnancy Considered from the Point of View of Prognosis and Conduct of Labor, Rev. franç de gynéc. et d'obst. 37: 916, 1938.

Twin pregnancy occurs once in 84 labor cases and two-thirds of them are found in multiparas. Rarely does a twin pregnancy go to full term. Most of them terminate in the eighth month. Abortion occurs in about 10 per cent. The most frequent complications of twin pregnancy are albuminuria, hydramnios, and eclampsia. Generally the second twin gives more trouble during delivery than the first. Spontaneous delivery took place in only 53 per cent of the cases of this series. The maternal death rate was 1.3 per cent and the fetal mortality was 18.5 per cent for the first twin and 23 per cent for the second twin. The prognosis of twins depends upon the degree of prematurity and the operative interventions.

The maternal and fetal prognosis was improved when both babies were delivered within less than fifteen minutes.

J. P. Greenhill.

CONCOMITANT RUPTURED ECTOPIC PREGNANCY, HYDROPS OF THE GALL BLADDER, AND OVARIAN CYST

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A SURVEY of the literature reveals a case in which ruptured ectopic pregnancy was associated with acute cholecystitis (Eisenklam) and one case in which ruptured ectopic pregnancy was associated with chronic cholecystitis and cholelithiasis (McKay). Numerous cases have been reported in which unilateral ovarian cysts were present in ruptured ectopic pregnancy and an occasional case of this condition combined with bilateral ovarian cysts has been described. The combination noted in the title of this paper has not been previously recorded.

The patient was a 24-year-old white woman who was admitted to the West Baltimore General Hospital, June 15, 1938, complaining of pain in the right lower quadrant of three days' duration. The last regular menstrual period began thirteen days prior to admission and lasted for six days. The patient began to bleed slightly from the vagina six days before coming to the hospital. This bleeding had gradually increased and had been profuse for two days. Three days before admission, dull steady pain began in the right lower quadrant and became pregressively worse. On the day she entered the hospital, the pain became much more severe and the appetite was impaired. She did not vomit or feel nauseated. There was no right upper quadrant pain. The patient explained that she "was menstruating fifteen days too early."

The gastrointestinal history revealed that there had been pain in the epigastrium for a year which came on about an hour after meals and was relieved by self-induced emesis. The patient had had frequent belching, but no "spells of vomiting" had occurred. There had been no pain under the "shoulder blade," jaundice, constipation, abnormal stools or hemorrhoids. Cardiorespiratory history showed some shortness of breath during her second pregnancy. Genitourinary history brought out the fact that the patient had had a nocturia for six months. Menstruation began at the age of 16. The periods occurred every twenty-eight days and lasted for six days. She was married seven years ago and has two children, both in good health. There have been no other pregnancies.

The patient was a well-developed and nourished woman of stated age, who was lying quietly in bed in no acute pain. The temperature was 100° F., the pulse 100, and the respirations 22. The blood pressure was 135/88. She was in unusually good spirits. Abdominal examination revealed doubtful right upper quadrant rigidity. A mass was present in the gall bladder region which extended from 6 to 7 cm. below the right costal margin downward about 8 cm. toward the umbilicus. At this point the mass, which was 4 cm. in cross diameter, was lost in the border of the right rectus muscle. On pelvic examination, a mass about the size of a lemon was felt in the right adnexal region. A doubtful fullness was felt in the left adnexal region.

Laboratory examinations disclosed a negative urine and an erythrocyte count of 5,100,000. A leucocytosis of 12,000 with 72 per cent polymorphonuclear cells was present. The blood Wassermann was negative. On the day following admission, the leucocyte count was 11,000 with 68 per cent polymorphonuclear cells and the blood sedimentation rate was 15 mm. (Wintrobe method after correction).

The patient was observed for three days and during this time she complained of moderate right lower quadrant pain. Her temperature and pulse were normal and her morale was good. The preoperative diagnosis was chronic pelvic inflammatory disease.

On June 18, operation was performed under seconal nitrous oxide and ether anesthesia. A lower midline incision was made and the exposed peritoneum was

seen to have a bluish color. When this was opened, about 250 c.c. of liquid and clotted blood was found in the pelvis. A large clot was present about the fimbriated end of the right tube, and when this was removed a point of rupture was seen about one inch from the opening (Fig. 1). The left tube was thickened and slightly injected and an ovarian cyst about the size and shape of a small orange was present. A bilateral salpingectomy and a left oophorectomy were done. The blood in the peritoneal cavity was evacuated. The appendix was removed. Routine palpation of the gall bladder at this time showed it to be greatly enlarged so that it extended to the region of the umbilicus. The primary incision was closed and an upper right rectus incision was made. One hundred cubic centimeters of white bile was evacuated from the gall bladder by paracentesis and a stone about the size and

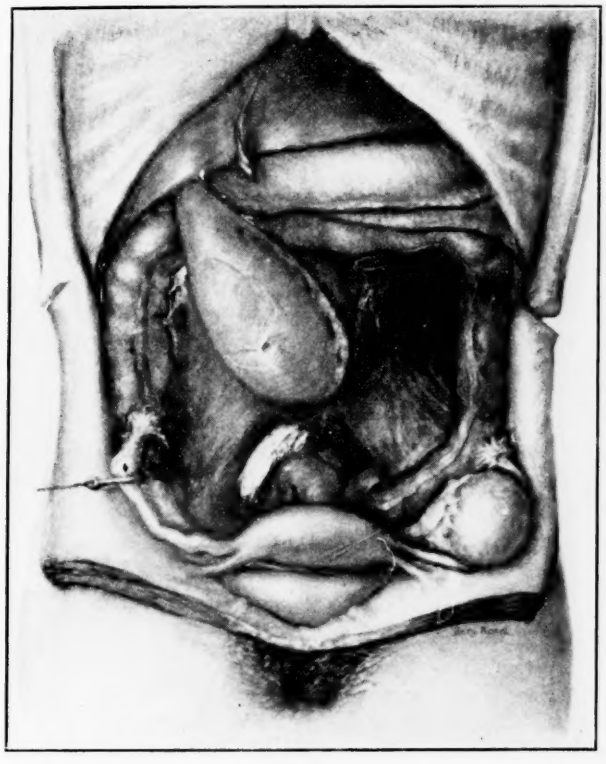

Fig. 1.

shape of a robin's egg was palpated in the cystic duct. The gall bladder was removed from below upward. A cigarette drain was placed in the foramen of Winslow. A smooth convalescence occurred and the patient left the hospital on the sixteenth postoperative day. She has been followed for about six months. Since leaving the hospital it has been possible for her to do her own housework. She had slight epigastric pain on one occasion, but this was relieved by taking cascara. Cascara is taken about once a week for constipation. There has been no emesis and her belching has been much less pronounced. No indigestion with "fatty foods" has been experienced. The patient did not menstruate the first month following the operation. Her period was three days late the second month and they have been regular since that time. She has had occasional twinges of the lower abdominal pain.

The pathologic report was hydrops of the gall bladder with acute cholecystitis, ruptured ectopic pregnancy, ovarian cystoma, chronic salpingitis, and chronic appendicitis.

The symptoms and signs of the present case are atypical of all three conditions found at operation. The case well illustrates the degree of pathology which may be present and still produce few symptoms. It also brings out the confusing picture which ectopic pregnancy may present even after rupture has taken place. The clinical picture of this condition is very frequently not characteristic.

A PHENOMENAL SINGLE OVUM TWIN PREGNANCY

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THIS case of a single ovum twin pregnancy presents features which, from a clinical and pathologic standpoint, are interesting and puzzling. We propose, therefore, to record both aspects of the case in some detail.

CASE REPORT

H. T., a white, 19-year-old primigravida, entered the St. Louis Maternity Hospital on Nov. 7, 1937, in active labor. From her menstrual history she was six weeks from term. She received her prenatal care at a municipal clinic and was diagnosed a twin pregnancy, which was confirmed by x-ray examination. The patient had not been to the clinic for over a month. She stated she had suffered severe headaches and had noticed some edema of the extremities during the week previous to admittance. At the time of entry to the hospital, she showed pitting edema of the ankles, but there were no other significant physical findings. The blood pressure was 130/80. Urinalysis revealed a two-plus albumin, but was otherwise negative. The pelvic measurements were normal. The patient was hastily admitted to the delivery room, since the head was visible at the vulva. Twenty minutes later the first baby was born spontaneously, following a right mediolateral episiotomy. The second baby, a full breech presentation, was also born spontaneously five minutes afterward. The third stage of labor lasted five minutes. The puerperium was uncomplicated and the patient was discharged from the hospital on the tenth post-partum day.

The first of the single ovum twins to be delivered was a macerated male stillborn, weighing 2,360 gm. The other twin was then delivered without difficulty. The cry and respirations were spontaneous. The infant was quite plethoric; the skin presented a deep bluish red color over the extremities and face, and an intense hyperemia over the trunk. Immediately following birth, the temperature dropped to 35.7° C., and moderate respiratory difficulty was noted. These symptoms rapidly disappeared with routine CO_2 and O_2 inhalations and elevation of body temperature. However, the color of the skin was unchanged. The only pathologic findings, aside from the abnormal color of the skin, were a slightly enlarged spleen and liver. The birth weight was 2,100 gm., the occipital frontal circumference was 32 cm. and the length 44 cm. After the first two days, the infant became quite active, taking its feedings eagerly and doing unusually well without the customary routine premature care required for newborns of this birth weight. There was no evidence of intracranial, pulmonary or cardiac abnormality. The Kline and Wassermann tests on mother and baby were negative.

On Nov. 9, 1937, the second day of life, because of persistent hyperemia of the skin, a red blood cell count was done and found to be 8.2 million. The following day, the red blood cells had dropped to 7.68 million. The hemoglobin was 18.0 gm. (Sahli). The white blood cell count was 2,500, stabs 3, segments 21, lymphocytes 76; all apparently normal cells. No erythroblasts were seen. The platelets appeared to be markedly reduced. The bleeding time was normal (two minutes).

The clotting time was definitely prolonged (twenty-four hours plus). At no time were there any hemorrhagic manifestations.

On the fourth day, 20 c.c. of blood were removed for study. On the following day another 20 c.c. were removed, for the possible benefit of combatting the polycythemia by lowering the blood volume. From the first sample, only sufficient serum could be recovered to perform the Kline test. The second sample of blood was centrifuged for five hours at high speed, but no serum was obtained. The blood was unusually thick and gelatinous in consistency. At no time was the infant dehydrated; however, daily subcutaneous injections of lactate-Ringer's solution were given, in an effort to dilute the blood. By the seventh day of life, the red blood cell count had fallen to 6.56 million and the skin had lost its bluish red color, appearing only moderately hyperemic. The platelet count was 32,600. On the following day, the red blood cell count was 6.2 million, the white blood cell count was 10,000 and differential: juveniles 2, stabs 23, segments 15, lymphocytes 58, monocytes 2, and reticulocytes 3.0 per cent. The clotting time had dropped to twenty minutes. The urine showed a trace of albumin, but no cells. At one month of age, the red blood cells had fallen to 5.76 million. The platelets rose to 576,000, the white blood cell count was 12,100 with a normal differential. Clotting time was ten minutes and bleeding time three minutes. The skin had returned to its natural color. X-rays of the long bones showed no abnormality. The infant was discharged on Dec. 15, 1937, weighing 3,100 gm., a gain of one kilogram in thirty-eight days.

When the patient was again seen, at the age of three months, the red blood cell count was 5.0 million. The spleen was not palpable, and the infant's growth and development were normal for its age.

Grossly, the placenta was that of a twin pregnancy, measuring 26 by 21 by 2 cm., and weighing 1,150 gm. The fetal surfaces were smooth and glistening. Both cords were eccentrically attached, the one from the viable baby being edematous. The septum between the fetuses was composed of two layers of amnion. The maternal surface showed a sharp line of demarcation between the placental tissue supplying the fetuses. Fig. 1, *A* shows the portion of the placenta which nourished the macerated stillborn, having an ischemic appearance, but otherwise normal. Fig. 1, *B* shows the portion of the placenta supplying the viable infant having a deep purplish red color, the gross picture of red infarction.

A section through the junction of the red and gray areas, Fig. 1, *C*, shows a very unusual microscopic picture (Fig. 2), which is described in the legend. Fig. 3 is a high power photomicrograph of the area of placenta attached to the dead fetus, labeled *A*, Fig. 1, and shows hydropic degeneration and avascularity of many of the villi. Other villi show poor vascularization. Some of the villi are still covered by both trophoblastic layers, Langhans' and syncytial cells, even though the pregnancy is of thirty-four weeks' duration. The part of the placenta described as *B*, Fig. 1, nourishing the viable infant, shows the fetal vessels markedly distended with blood and in many areas the vessel walls have ruptured and the blood has extravasated into the stroma of the villi, being confined only by the syncytial covering. The villi are closely crowded with inadequate intervillous spaces. Fig. 4 shows a high power photomicrograph of this area. A section through the septum between the fetuses, which is composed of two amniotic membranes, corroborates the gross diagnosis of a single ovum twin pregnancy.

DISCUSSION

The blood changes which occurred in the living infant are difficult to explain satisfactorily. It is suggestive that similar, but more pronounced blood changes were present in the macerated twin, which, indeed, may have accounted for its death, but unfortunately a post-mortem examination was refused. The polycythemia cannot be explained on the basis of anhydremia, in view of the absence of dehydration and lack of concentration of other blood elements.

It is probable that the abnormal hyperemia of the skin and mucous membranes was secondary to engorgement of the capillaries with erythrocytes, since the skin became normal in color when the red blood cells dropped within normal range. The

absence of pulmonary, cardiac, or umbilical cord abnormalities was against a circulatory disturbance as a cause of the plethorism. The possible exogenous causes which might result in a defective oxygenation of the blood were ruled out.

The presence of other findings suggests that the abnormal increase in red blood cells originated within the fetal tissues. These findings are: leucopenia, thrombocytopenia, marked prolongation of the clotting time, thick gelatinous blood, with a relative or actual decrease in serum content, and unusual changes in the placenta.

The placenta showed many interesting and unusual findings. In the first place as stated above, it was a single ovum twin placenta. Due to pathologic changes arising in the fetal blood vascular systems, there was a sharp line of demarcation between the two portions of the placenta supplying the fetuses. It is well known that the fetal vessels grow down through the umbilical cord and unite with those from the placenta which arise in situ in the villi. It is, therefore, easy to see that the chorionic villi destined to become the chorion frondosum are divided between the two fetuses, but it is unusual to find these portions so clearly defined.

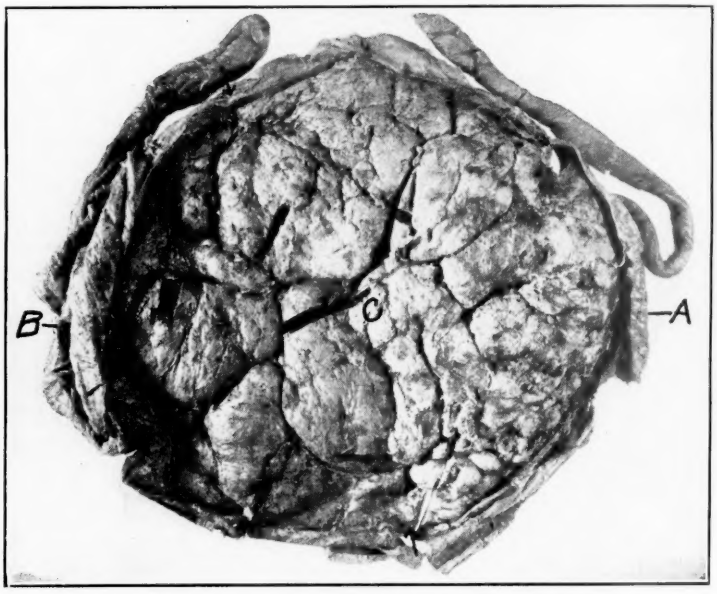

Fig. 1.—*A* indicates the ischemic portion of the placenta which nourished the macerated stillborn fetus. *B* designates the deep purplish red portion of the placenta which nourished the living infant.

Not so easily explained are the gross picture of ischemia; the microscopic picture of avascularity, hydropic degeneration of many of the villi and the persistence of Langhans' cells up to thirty-four weeks' gestation in the placenta of the macerated fetus (Figs. 1, *A* and 3). As indicated above a similar but more profound blood dyserasia may have existed which caused the fetus to perish, and the placental pathology may be secondary to fetal death. We have seen repeatedly this picture in placentas, which have been retained in utero after the death of the fetus from any cause. The viability of the chorionic tissue is dependent on maternal and not on fetal circulation, as exemplified in cases of early villi before fetal vessels have formed and in cases of hydatidiform mole, where there is an absence of fetal vessels, yet there is marked proliferation of the trophoblast. The prolonged viability of the placental tissue is thus explained. The fetal circulation stopped with the death of the fetus, and the vessels became obliterated. Therefore the placenta had an anemic appearance. There was no evidence of white infarction. Of course, it

Fig. 2.—This is a low power photomicrograph of an area at the junction of the two portions of the placenta, designated *C*, in Fig. 1. *A*, represents the portion attached to the stillborn, and shows large hydropic villi and *B*, defines the part of the placenta supplying the living infant and clearly pictures marked congestion of the vessels of the villi.

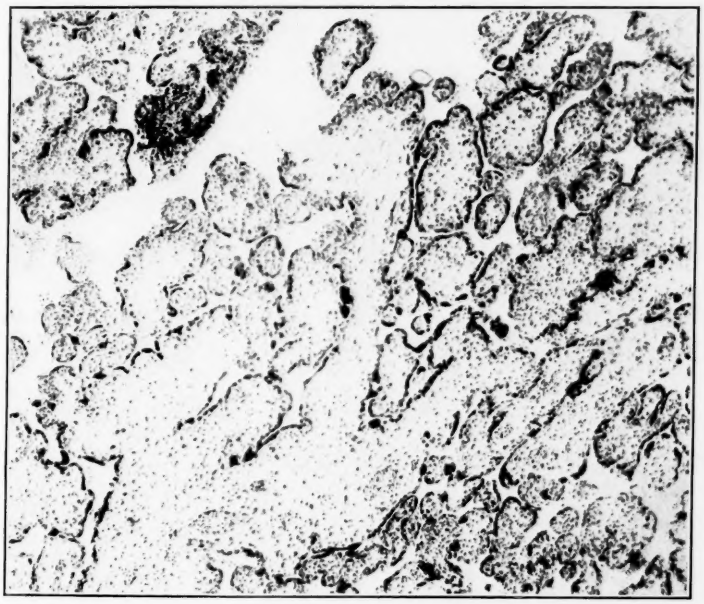

Fig. 3.—A high power photomicrograph of the area of the placenta attached to the stillborn fetus. Note the hydropic villi, some avascular, others poorly vascularized. In some villi both trophoblastic layers are distinguishable.

is possible that some other cause may have existed to produce the death of the fetus, and the same picture would be present.

Ordinarily Langhans' cells disappear from the villi from eighteen to twenty weeks. We have never seen them persist so long a time as this. Their function is not known, but it is thought they have something to do with metabolism, since they disappear after the placenta is well developed. Perhaps the baby died before the usual time for these cells to disappear (eighteen to twenty weeks) and there was no further development of this portion of the placenta. However, the weight of the baby (2,360 gm.) would indicate that it was viable for a much longer time.

The gross picture of marked congestion and the microscopic picture of red infarction in the portion of the placenta nourishing the viable fetus (Figs. 1, *B* and 4) is not actually red infarction. Placental infarction is produced by cutting off the maternal circulation, either arterial or venous. Because of this interference the trophoblast is injured by the lack of oxygenation and by a collection of noxious metabolic products from the fetus. As a result of the damage to the epithelium of the villi, there is a response to tissue injury on the part of the capillaries of the villi. The vessels of the villi are turgid with blood and at times become dilated to

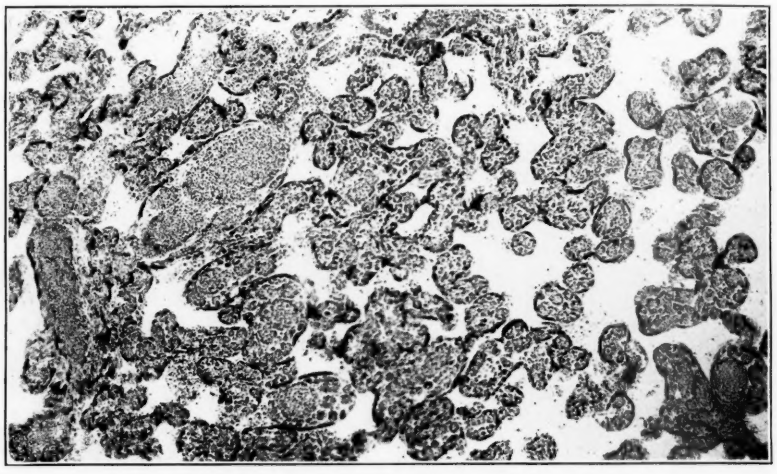

Fig. 4.—A high power photomicrograph of an area of the placenta supplying the living infant. The fetal vessels are markedly engorged and have ruptured in places so that the blood is confined by the syncytial covering. The villi are closely crowded with comparatively little intervillous spaces.

the point of rupture. In this case the whole of that portion of the placenta supplying the viable infant showed this change, and it would be incompatible with the life of the fetus if it were red infarction. We, therefore, sought another explanation of this pathologic picture. We believe the picture in the placenta is secondary to the unexplained, temporary polycythemia in the fetus. The fetal circulation was so engorged from the increase in blood volume that the vessels of the villi were markedly dilated and in many instances the pressure was so great that the vessels could not withstand it and rupture occurred with extravasation of blood into the stroma of the villi. The maternal circulation was intact so that nourishment could be carried to the fetus and excrementious materials removed.

SUMMARY

A single ovum twin pregnancy is reported showing the following salient points:

1. One twin was a macerated, male stillborn, weighing 2,360 gm.

2. The other twin weighed 2,100 gm. The infant was quite plethoric and the skin was a bluish red color. The baby was found to have polycythemia. The red blood cell count was 8,200,000. The white blood cell count was 2,500. The platelets were reduced to 32,600. The bleeding time was normal. The clotting time was defi-

nitely prolonged. The red blood cell count gradually dropped until it was 5,760,000, at the end of the first month of life. The platelet count mounted to 576,000 at the same period of time. The baby was discharged thirty-eight days after birth, weighing 3,100 gm. and in apparent good health. At three months of age, the child was perfectly normal for his age.

3. The placenta was that of a single ovum twin pregnancy. The portion that had supplied the stillborn infant was grayish white in color and that nourishing the viable infant was bluish red in color, a startling contrast in the division of the placental tissue between the fetuses. We believe the pathologic changes in the portion of the placenta which had nourished the stillborn are secondary to the death of the fetus. It is suggested that the fetus may have died from a blood dyscrasia, similar to that of the viable twin. The unusual congestion in the placenta nourishing the living infant was considered to be secondary to temporary changes in the hematopoietic system of the baby.

HIDRADENOMA OF THE VULVA*

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DURING the past ten years, we have seen five cases of hidradenoma of the vulva at the Jewish Hospital of St. Louis. In view of the fact that these cases are comparatively rare, about 40 in the literature with only 2 case reports from America,[1, 2] and as there is some question of the potential malignancy of this tumor, we felt that it was worth while to describe our cases and summarize the findings of others. Our cases are of further interest in that they seem to present various stages in the development of the tumor.

Werth, in 1878,[3] and Schickele,[4] in 1902, reported cases which undoubtedly were hidradenomas of the vulva; both assumed that the tumor arose from aberrant epithelium. Werth mentioned no specific anlage while Schickele believed that they arose from remnants of Wolffian ducts because of the resemblance to kidney, testicle, and Wolffian structures in general. Landsteiner[5] and others contended that these tumors may represent aberrant mammarian tissue. Braun,[6] in 1892, was the first to call attention to the possibility of formation of adenoma of the sweat glands of the vulva. It remained for Pick,[7] in 1904, to point out the true nature of these tumors. He believed that they were in all probability congenital in origin and derived from malformed sweat gland anlage. He based his ideas on the resemblance of the morphologic traits of the hidradenomas to those of the normal sweat glands which consisted especially of the double-layered character of the epithelium and the presence of a membrana propria elastica around the tubules of the adenoma. Pick classified the adenomas of the sweat gland as hidradenoma tubulare, which are derived from mature sweat glands; hidradenoid adenoma, which are derived from epidermis or rudimentary sweat glands; and a combined form. The histologic structure of both the hidradenoma tubulare and the hidradenoid adenoma is similar, the difference being in that the former contains a sudoriferous duct which would tend to show that it arose from a fully formed sweat gland, whereas the latter is lacking in such proof. We believe, as do Landsteiner and Outerbridge, that Pick's classification complicates matters and that the single term "hidradenoma" should be used.

CASE REPORTS

CASE 1.—Mrs. E. W., aged 48 years, gravida i and para i, was seen on Sept. 17, 1938. The patient had noticed a small nodule in the furrow between the right labium

*This work aided by the David May-Florence G. May Fund.

majus and minus, just below the level of the clitoris. She had been aware of the nodule since she was in her teens. However, it did not start to grow until the month previous to excision. When it was excised on Sept. 19, 1938, it was the size of a pea, soft in consistency, freely movable and not painful or tender. A preoperative diagnosis of hidradenoma of the vulva was made.

Histologic Examination (Fig. 1).—The intact squamous epithelium lay just above the tumor. There was a thin, but definite connective tissue capsule with a few scattered sweat glands in the periphery. The lesion itself was composed of papillomatous proliferations within a cyst. The proliferations branched and gave the tumor the appearance of a labyrinth in some areas. There was a thin connective tissue core to the proliferations which were lined by a single layer of cuboidal or columnar epithelium. The cell boundaries were not definite, but the nuclei were clear, large, oval, or round in shape, and basically situated. The epithelium also formed acini which were of varying size and shape. A few of the acini were distended with secretion and had a flattened epithelium; others were lined by a double layer of cells, an inner columnar or cuboidal, and an outer flat or spindle layer. There were a few groups of cells in the connective tissue stroma which resembled those of the lining epithelium, but which showed no evidence of gland formation. However, there was no impression of malignancy.

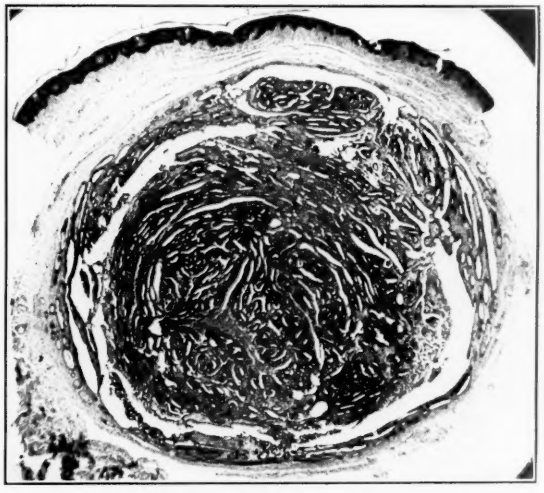

Fig. 1.—Case 1. The tumor is situated in the corium beneath the intact squamous epithelium and consists of papillary proliferations within a cyst.

CASE 2.—Mrs. E. K., aged 55 years, gravida iv and para iii, entered the hospital on Aug. 23, 1937, because of diabetes, hypertension, and a right inguinal hernia. She had had a vaginal hysterectomy for a fibroid uterus on Sept. 16, 1925. The lesion on the vulva was found during a routine examination. The nodule was located in the midline of the fourchette, being about 0.5 cm. in diameter. It was fixed to the vaginal mucosa and appeared to have a very shallow ulceration. A senile vaginitis and kraurosis and leucoplakia of the vulva were also present. The inguinal glands were palpable and firm. A biopsy was performed on Aug. 5, 1937, and a wide excision on Aug. 24, 1937.

Histologic Examination.—This tumor lay just beneath the squamous epithelium and was composed of papillary proliferations and acini similar to those described in Case 1. It had a lobulated appearance with distinct evidence of intracystic proliferation in only one of the lobules. There was no definite connective tissue capsule, but the lesion was well demarcated without evidence of malignancy. In one area the epithelium was composed of large, pale, cylindrical cells closely resembling those of the apocrine and mammary glands. At the periphery of the tumor, there were areas of round cell and plasma cell infiltration and a few sweat glands.

CASE 3.—Mrs. B. D., aged 45 years, gravida iii and para iii, entered the hospital on Jan. 24, 1934, for excision of a tumor that had been discovered accidentally on the left labium majus. It was about the size of a pea. The surface was ulcerated with well-defined margins. The tumor was solid on cut section.

Histologic Examination.—The squamous epithelium was ulcerated; the base and wall of the ulcer consisted of the well-circumscribed tumor mass. A very thin layer of concentric connective tissue fibers and a few areas of mild plasmocytic infiltration were present about the periphery. A ball of hyalinized connective tissue was located near the center of the tumor. There were areas in which the acini were lined by a double layer of epithelium and areas in which there were strands of epithelial cells in the stroma. Otherwise the tumor was similar in appearance to those described above.

CASE 4.—Mrs. A. J. R., a private patient of Dr. J. H. Armstrong, aged 58 years, was seen on June 11, 1934, with the history of having noticed a swelling of six months' duration on the right labium minus. It was about the size of a pecan. The tumor was excised on June 18, 1934. In January, 1937, this patient had a radical operation for cancer of the breast.

Histologic Examination.—This lesion showed areas of cyst wall which were composed of fibrous tissue lined by a flattened epithelium. The proliferations, however, protruded beyond the level of the squamous epithelium. The tumor was otherwise as described in the previous cases and here, too, there are small areas of cells resembling those of the mammary glands.

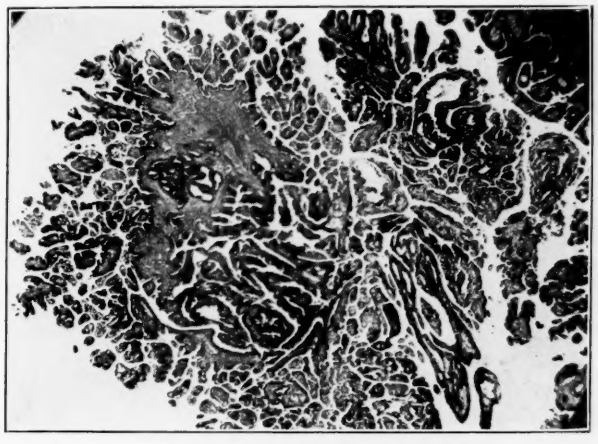

Fig. 2.—Case 5. The tumor consists of a polypoid growth with a marked increase in the connective tissue.

CASE 5.—Mrs. I. S., a patient of Dr. J. Orenstein, aged 49 years, gravida iii and para iii, was seen on May 5, 1936, with the history that during the past year she had noticed a small tumor on the left labium majus which would bleed occasionally. Examination revealed a pedunculated tumor about the size of a pea which was ulcerated and bled on touch. The tumor was excised on May 5, 1936.

Histologic Examination (Fig. 2).—Sections through the pedunculated tumor showed a polypoid growth lined by the same type of epithelium described in the above cases, with areas of a double layer of cells. The stroma, however, showed a marked increase in the amount of connective tissue over those previously described. No capsule was present.

In reviewing 37 cases in the literature, plus the 5 cases of our present series, the following information has been obtained.

Most of the patients have come to operation when they were in their fifth decade; the youngest, however, was 25 years of age and the oldest was 62 years of

age. The distribution of the cases according to the age at which operation was performed is as follows:

AGE GROUP	NO. OF CASES
25 to 29	1
30 to 39	8
40 to 49	16
50 to 59	5
60 -----	1

A few of the patients gave the history of having noticed the tumor for some time before its removal. This was true in Case 1, the patient having noticed the nodule when she was still in her teens, but the lesion did not grow until one month before its removal, at the age of 46. Gross[8] reported a case in which the tumor was present in childhood and was removed at the age of 43, after it had been increasing in size over a period of one year. Of the few case reports that mentioned the duration of the tumor, the time intervals between observance and removal were: 2 years, 2 years, 6 months, 3 months, and 2 months. Frequently the tumors were discovered by the physician during the course of an examination.

The hidradenomas occur more frequently on the labium majus, as 32 tumors were found in this location with only 12 tumors reported elsewhere on the vulva. Seven of the latter were located on the labium minus; 3 were situated between the labium majus and minus; and the remaining 2 were found on the posterior commissure. There may be more than one lesion in the same patient. Cases of 3 and 4 nodules in one patient have been reported by Pick and Gross, respectively.

The lesion is usually about the size of a pea, slightly elevated, and round or oval in shape. However, the size may vary considerably, ranging from 3 mm. in diameter (Woringer[9]) to that of a walnut (Schroeder[10]). Blau[11] reports one case in which pregnancy did not influence the size of the tumor. In 5 cases (Pick, Hoeck,[12] Schiffman,[13] Koehler,[14] and our case (5) the lesion was a polyp or funguslike growth. In 5 cases, including 2 of the present series, the surface was ulcerated. In 2 of these, bleeding was produced on touch. The tumor may be covered with hair and in a few cases has been described as red or pink in color.

The hidradenomas may be either firm or cystic. Three cases of Eichenberg's and 1 of Schroeder's were markedly distended with fluid. In such cases the papillomatous proliferation fill only a part of the lumen, whereas, in others it fills the lumen completely, giving the tumor a firmer consistency. In no case was the tumor tender, painful, or adherent to the underlying structures. However, in 3 cases it was described as adherent to the skin.

Histologically, hidradenomas may take the form of cystic nodules in which the lumen of the cyst may be partially or entirely filled with papillomatous proliferations. Papillary proliferations are the usual picture; they may take origin from a broad base or from a single pedicle. In all of our own cases, the origin was apparently from a broad base. The tumor may have a labyrinthine or papillomatous appearance or both.

The acini vary in form, shape, and size. Some are dilated and contain an amorphous secretion. The epithelium is usually a single layer of tall columnar cells on a well-marked basement membrane. Each cell contains a vesicular nucleus situated near the base. The epithelium may also be cuboidal or consist of a double layer of cells. The inner layer consists of columnar cells and the outer layer of flat spindle or cuboidal cells. In one of the 13 cases reported by Eichenberg the epithelium was double-layered throughout. He was also the first to describe collections of cells which resembled those of the apocrine and mammary glands. This is understandable from the probable common embryologic origin of the mammary and sweat glands. He found these cells in 5 of 13 cases and we have found them in 2 of our series. In addition to acinar formation, there are usually present masses and columns of epithelial cells embedded in the stroma without lumen formation. This feature has caused some authors to believe that the hidradenomas are potentially or definitely malignant. We feel that some of these collections of cells, at any rate, may be tangential sections through the edge of acini.

The connective tissue supporting structure is usually scant and delicate, but may be markedly increased in amount as is illustrated in comparing the sections of Cases 1 and 5 (Figs. 1 and 2). Occasionally there are areas of dense acellular connective tissue as is demonstrated in Case 4. Eichenberg and Hoeck report cases with similar connective tissue changes. The connective tissue may form septa and give the tumor a lobulated appearance. The connective tissue capsule shows a marked variation. It is completely absent in some cases, and in others varies from an incomplete capsule of concentrically arranged fibers to one which is thicker and completely encircles the tumor. The lining epithelium of the cyst wall resembles that of the acini of the tumor proper and may be found to vary from a double layer of cells to a single layer of flattened cells. There may or may not be a round cell and plasma cell infiltration about the lesion. In some cases, sweat glands, many of which are distended, are found about the periphery.

We believe that the hidradenoma starts as a soft, cystic tumor with a small papillomatous growth arising from a portion of the cyst wall (Case 1). As the tumor grows, it fills up the entire lumen of the cyst, giving it a firmer consistency. With continued growth the tumor mass pushes its way toward the plane of least resistance which is beneath the squamous epithelium. The pressure against the skin results in an ulceration of the squamous epithelium, with the base and wall of the ulcer formed by the tumor. This stage is illustrated by Case 3. Finally, the growth rises above the epithelium, forming a funguslike or polyplike tumor, as is found in Cases 4 and 5. We do not believe that this continued growth eventually leads to malignancy, but rather that the tumors which are malignant show this tendency from the start. This belief is supported by the fact that in the one case which was definitely malignant, the tumor consisted of a papilloma within a cyst rather than a funguslike growth.

Early investigators pointed out that there was a close resemblance between hidradenomas and malignant adenomas. As a matter of face, Pick at first took them to be metastases of such growths. Schickele, who reported one of the first cases, considered the tumor malignant. However, it has since been rather definitely demonstrated that hidradenomas of the vulva are usually benign.

Of all the cases in the literature, only one, that of Eichenberg's, was definitely shown to have metastasized. This woman was 35 years of age. She developed a movable almond-shaped, cystic nodule on the left labium majus. Within the cyst was a papilloma. Microscopically this tumor showed a double layered epithelium with areas of marked epithelial proliferation and projection of strands into the surrounding tissue. The left labium was completely removed with the lymph nodes of the left inguinal region. In one small lymph node in the labium, metastasis was found. There were no recurrences of the tumor after two years.

Ruge[16] considered his tumor as definitely malignant, but both Burg[17] and Hoeck,[12] who reviewed his case, do not agree with him. Schwarz called his tumor an adenoma hidradenoides tubulare destruens because it showed destructive tendencies. In comparing his case with that of Ruge's, Schwarz believed that in the latter the evidence of invasiveness was less convincing than in his own. The other suspicious case was reported by Schiffman[13] in which there were no signs of penetration or of definite destructive tendencies, but the author believed that the irregularly arranged collections of polygonal cells within the tumor proper might be looked upon as a beginning carcinomatous degeneration. Outerbridge had considered his case as distinctly suspicious, but after more careful study was convinced that it was entirely benign.

In a follow-up of the 5 cases in our series, none were found to have evidence of a recurrence or metastasis after periods of 5 years, 4 years and 6 months, 2 years and 8 months, 1 year and 5 months, and 6 months. Outerbridge and Williamson[18] report no recurrence in their cases after 1 and 3 years, respectively. Woringer reported the only case of recurrence. The tumor was removed two years after the initial excision. Therefore, with the exception of the 1 definitely malignant case, and the 2 very doubtful ones, all hidradenomas of the vulva reported in the literature have had a benign course.

TREATMENT

Wide local excision of the lesion has been the usual method of treatment. In only 2 cases, both of which were suspected of malignant tendencies, was a more radical operation performed. One case was that of Eichenberg's in which an excision of the entire labium majus and an inguinal gland dissection of the corresponding side was performed. The other case was reported by Schwarz, who did a secondary excision of the labium.

CONCLUSIONS

Five cases of hidradenoma have been presented and 37 cases from the literature have been reviewed. We do not believe that this tumor is as rare as the number of cases in the literature would seem to indicate, but rather that in many instances these small tumors have been overlooked. Hidradenomas of the vulva are benign.

REFERENCES

(1) *Outerbridge, George W.:* Am. J. Obst. **72:** 32, 1915. (2) *Schwarz, Emil:* Am. J. Obst. & Gynec. **1:** 695, 1921. (3) *Werth:* Quoted by E. Schwarz.[2] (4) *Schickele, G.:* Beitr. z. Geburtsh. u. Gynäk. **6:** 449, 1902. (5) *Landsteiner, Karl:* Beitr. z. path. Anat. u. z. Allg. Path. **39:** 316, 1906. (6) *Braun, Heinrich:* Arch. f. klin. Chir. **43:** 213, 1892. (7) *Pick, L.:* Virchow's Arch. f. path. Anat. **175:** 312, 1904. (8) *Gross, E.:* Ztschr. f. Geburtsh. u. Gynäk. **60:** 565, 1907. (9) *Woringer, F.:* Bull. Soc. franc. dermat. & syph. **45:** 122, 1938. (10) *Schroeder, R.:* Centralbl. f. Allg. Pathol. u. path. Anat. **22:** 529, 1911. (11) *Blau:* Quoted by A. Taddei.[19] (12) *Hoeck, Werner:* Zentralbl. f. Gynäk. **50:** 2757, 1926. (13) *Schiffman, Joseph:* Zentralbl. f. Gynäk. **44:** 59, 1920. (14) *Koehler, R.:* Monatschr. f. Geburtsh. u. Gynäk. **44:** 493, 1916. (15) *Eichenberg, H. E.:* Ztschr. f. Geburtsh. u. Gynäk. **109:** 358, 1934. (16) *Ruge, H.:* Ibid. **56:** 307, 1905. (17) *Burg, E.:* Zentralbl. f. Gynäk. **54:** 395, 1930. (18) *Williamson, H.:* J. Obst. & Gynaec. Brit. Emp. **10:** 253, 1906. (19) *Taddei, A.:* Clin. ostet. **36:** 220, 1934. (20) *Meyer, Robert:* Ztschr. f. Geburtsh. u. Gynäk. **86:** 420, 1923. (21) *Fleischmann, Carl:* Monatschr. f. Geburtsh. u. Gynäk. **21:** 497, 1905. (22) *Stern, Robert:* Ibid. **39:** 707, 1914.

NEPHRECTOMY DURING PREGNANCY*

In a Patient With Pre-Existing Hypertensive Disease

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THE following report of a removal of the left kidney early in pregnancy has several unique features.

History.—The patient was a 31-year-old Jewish woman, married eight years, and pregnant for the first time. Her medical history had been uneventful until four years ago, at which time she had developed a toxic exophthalmic goiter. Her basal metabolic rate at the time was plus 80 per cent, and her blood pressure, though not elevated above the normal range, showed some widening of the pulse pressure. The treatment of her toxic goiter had been carried out at the University Hospital over the intervening four-year period, and had consisted of three operations upon the thyroid gland and a course of x-ray therapy. During this time her toxic symptoms had subsided, but she had gradually developed a marked and fixed arterial hypertension.

At the time of her first obstetric examination she was eight-weeks pregnant. Blood pressure was 190, over 130, and her pulse rate was 100. There were no obvious

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residual phenomena referable to her thyroid gland except exophthalmos. At this time it was discovered that she had a large firm tumor occupying the left side of the abdomen, apparently fixed beneath the left costal margin and extending downward to the level of the left anterior superior spine of the ilium. Radiologic and urographic studies showed that the tumor involved the left kidney. Renal function studies indicated that excretory function was normal in the opposite kidney. The tentative diagnosis of the tumor was hypernephroma. Because the patient desired that everything possible be done to preserve her pregnancy, it was decided that surgical removal of the tumor should be attempted without preoperative irradiation.

A left nephrectomy was successfully performed in the sixteenth week of pregnancy by Dr. Alexander Randall through a left lumbar incision. The tumor and affected kidney measured 31 by 22 by 17 cm. Histologic examination confirmed the diagnosis of hypernephroma.

After an uneventful recovery from her operation the patient was examined at frequent intervals during the remainder of her pregnancy, which continued to the thirty-fifth week. She was admitted to the hospital on three occasions during this time for periodic checkup of renal function, and for the control of her hypertension, which gradually became more elevated as the pregnancy advanced. It was felt advisable to terminate her pregnancy, because in addition to gradually mounting blood pressure, and a significant rise in the blood urea nitrogen, a moderate albuminuria (0.8 gm. per 24 hours) had appeared by the thirty-third week. Renal concentrating function was normal.

Pregnancy was terminated in the thirty-fifth week by an elective cesarean section under local anesthesia. A premature (2,130 gm.) living infant was obtained. The mother's postoperative course was uneventful, and the threatening signs of renal decompensation which had developed just before delivery rapidly disappeared. Mother and infant left the hospital in good condition.

The patient's arterial hypertension has remained fixed in the twenty-one-month period since her delivery. She has shown no impairment of renal function. During the same period there has been no demonstrable recurrence or metastasis of the hypernephroma.

COMMENT

The combination of hypernephroma and pregnancy is rare. Equally rare is the opportunity for observing the effect of pregnancy upon an established hypertensive disease in a patient deprived of one kidney. Interest was centered upon this second aspect of the above case, because of the potential importance of the lessons to be derived therefrom.

The studies of Matthews[1] and of Prather and Crabtree[2] have shown that in nephrectomized pregnant women, the essential problem is the behavior of the remaining kidney in the third trimester of gestation. Although the majority of 365 such pregnancies studied by Prather and Crabtree progressed normally, a significant number of patients developed renal complications. Three women died in uremia, and one in eclampsia.

The data of Prather and Crabtree, however, are based upon cases in which the blood pressure was presumably normal at the beginning of pregnancy. Information concerning two nephrectomized pregnant women in whom there had been a preexistent arterial hypertension is recorded by Henriksen and Spence[3] and by Melick.[4] One of these patients developed eclampsia, while the other went through her pregnancy uneventfully.

The fixed hypertension in our case was ascribed to a benign nephrosclerosis. The height of the prepregnancy blood pressure was formidable enough to have warranted caution in permitting pregnancy to continue even in a patient possessing both kidneys. The outcome of the case, however, demonstrates that pregnancy may occasionally be carried to the period of viability in this disease in spite of the removal of one kidney.

The absence of demonstrable impairment of renal function two years after delivery in a case like this furnishes no clue to the cost of the pregnancy in terms of permanent kidney damage. It would be difficult to believe that the renal stress

which is so often manifested when pregnancy complicates chronic hypertensive syndromes does not accelerate the underlying vascular or renal disease. On the other hand, there are no studies of the life history of such disease which evaluate satisfactorily the influence upon it of factors other than pregnancy, and which might be used as controls in attempting to appraise more precisely the deleterious effects of pregnancy alone. Such studies are greatly needed for comparison with the pertinent studies of Stander and Peckham[5] and of Corwin and Herrick[6] relating to pregnancy in hypertensive disease.

SUMMARY

A case of hypernephroma of the left kidney complicating pregnancy is reported. Its unique features are as follows: (1) The existence of a benign nephrosclerosis with fixed arterial hypertension prior to the pregnancy and the discovery of the tumor. (2) Removal of the tumor and affected kidney in the sixteenth week of pregnancy, without effect upon the hypertension. (3) Successful maintenance of the pregnancy beyond the period of viability, and the delivery of a child which has survived. (4) Absence of evidence of acceleration in the patient's renal vascular disease twenty-one months following the childbirth.

REFERENCES

(1) *Matthews, H. B.:* J. A. M. A. **77:** 1634, 1921. (2) *Prather, G. C., and Crabtree, E. G.:* Trans. Am. Assn. Gen.-Urin. Surg. **26:** 313, 1933. (3) *Henriksen, E., and Spence, J. M.:* J. A. M. A. **108:** 1866, 1937. (4) *Melick, J. M.:* Am. J. Obst. & Gynec. **37:** 334, 1939. (5) *Stander, H. J., and Peckham, C. H.:* Ibid. **22:** 626, 1931. (6) *Corwin, J., and Herrick, W. W.:* Ibid. **14:** 783, 1927.

OVARIAN PREGNANCY

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THE occurrence of ovarian pregnancy was generally conceded until Velpeau, in 1835, questioned the authenticity of cases that had been reported as such. In 1878, Spiegelberg laid down definite requirements, which must be met before such a diagnosis can be justified. These are, (1) that the tube on the affected side be intact, (2) that the fetal sac occupy the position of the ovary, (3) that it must be connected with the uterus by the ovarian ligament and (4) that definite ovarian tissue must be found in its wall.

Since Thompson's case, in 1902, there has been an increasing number of true ovarian pregnancies described, but at the same time, the comparative rarity of its occurrence is recognized. Remembering that rupture of the sac at an early period may occur, or that degenerative changes may occur at an early period without rupture, it is probable that a goodly number are not recognized as such.

CASE REPORT

R. C., aged 27 years, para i, was admitted Oct. 25, 1937, complaining of pain in the lower left quadrant of the abdomen, of one month's duration, had had similar pain in 1932, which caused her to remain in bed for two weeks. Menses were regular and normal. Last period began Oct. 16, 1937, five days and no pain. She had a normal spontaneous labor, at term, in 1928.

Physical Examination: Chest normal, blood pressure 118/70, abdominal palpation showed tenderness over left pelvic area, vaginal outlet was parous, cervix was hypertrophied with widened and reddened external os. The fundus was anteriorly placed and mobile, but slightly enlarged and irregular in outline. Moderate-sized

masses were felt in both adnexal regions and both were tender. The urine was normal. Hg 75, red blood count 3,850,000, white blood count 6,600.

At operation, Oct. 27, 1937, the mass, 6.5 by 6 cm., in the left pelvis was found to be immobile and covered by omentum, which was firmly attached. This was liberated and when attempt was made to free and mobilize the mass a fetus 5.5 cm.

Fig. 1.—Ovarian cortex (magnification 80 diameters) showing follicle cyst and hemorrhage throughout stroma. Section was taken through most normal looking portion of ovarian tissue surrounding placental tissue.

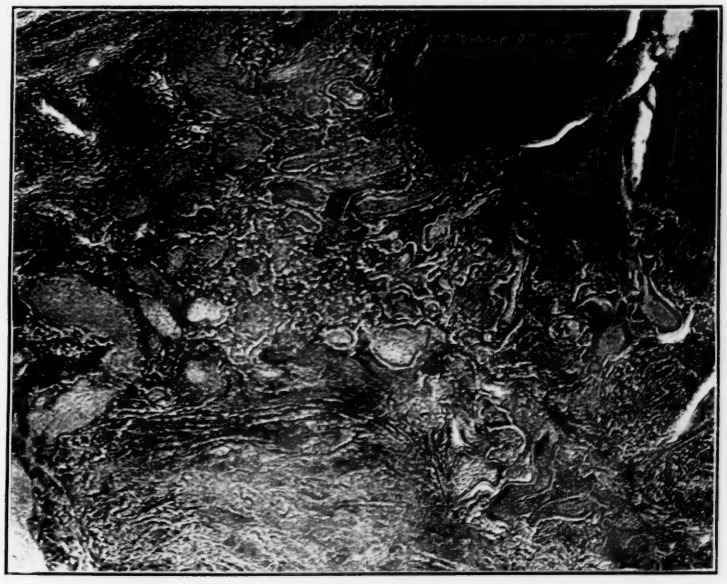

Fig. 2.—Placental tissue and blood clots (magnification 80 diameters), showing numerous necrotic placental villi embedded in blood clots.

was extruded through the wall of the mass. The right pelvis contained a simple cyst of the ovary, 5.5 by 5 cm. The fundus showed several small myomatous nodules. A supravaginal hysterectomy and bilateral salpingo-oophorectomy was done.

Pathologic Report.—(Hosp. Case 81,333, Specimen No. 14,129.) (a) Uterus 65 by 60 by 49 mm. (supracervical hysterectomy), containing several small fibroids, the largest one being 18 mm. in diameter. Endometrium congested, uterine cavity of normal size. (b) Right tube 55 by 11 mm. with the distal end obliterated. (c) Left tube 59 by 12 mm. (d) Left ovary 85 by 65 by 50 mm. consisting of a more or less uniform mass, intensely hemorrhagic and grossly necrotic. The mass was surrounded by a thin walled capsule containing occasional compressed follicle cysts. (e) Right ovary, cystic, consisting of one simple serous cyst, 55 by 50 by 45 mm. (f) Moderately macerated fetus, 5.5 cm. long.

Histopathologic Diagnosis.—(a) Multiple, small fibroleiomyomas without degenerative changes. Moderately hemorrhagic endometrium in follicular phase. Several small fibroleiomyomas were present, without evidence of degeneration. The endometrium showed occasional areas of hemorrhage, all of them placed very superficially. The glandular pattern was of follicular type. (b & c) Chronic salpingitis. There was a mild diffuse fibrosis involving the tube wall and mucosa, the stroma of the latter being moderately thickened. Focal accumulations of lymphoid cells were found throughout mucosa and musculature. (d) Ruptured ovarian pregnancy. The left ovary consisted of a small shell of ovarian cortex containing occasional compressed, distorted follicle cysts, partly filled with old blood. The rest of the ovarian mass consisted of old blood clots and necrotic placental tissue, the latter being almost completely autolyzed. (e) Simple serous ovarian cyst. The ovary was occupied by a simple serous cyst (small), the wall of which consisted of fibrous connective tissue with occasional small retention cysts. The lining of the cyst was smooth, the cells being of the benign type. (f) Fetus. No sections were made through the fetus as it was deemed desirable to save specimen intact.

The pathologic examinations were made by Dr. Tomás Cajigas, M.D., Pathologist, Columbia Hospital for Women, Washington, D. C.

SUMMARY

An unusual case of ectopic pregnancy, without history or symptoms indicative of pregnancy.

Arrest of development and retention of fetus in sac.

Specimen conforms to requirements of Speigelberg, plus recovery of fetus in situ.

CARCINOMA OF THE CERVIX IN A GIRL OF NINETEEN YEARS

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THE extreme rarity of carcinoma of the cervix in the young has been shown in previous publications by Bonner[1] in 1927, Morse[2] in 1930, and Baldwin[3] in 1931. The last case report was published in 1936 by Ludwig[4] who quotes the statistics of the previous authors, covering a period of forty-eight years. They found only 6 authentic cases of patients with cervical carcinoma between the ages of 16 months and 14 years, and 7 patients between the ages of 16 and 20 years. Ludwig's case and the case reported here make a total of 9 patients with carcinoma of the cervix between the ages of 16 and 20 reported in the literature over a period of more than 50 years.

CASE REPORT

A colored female, married, aged 19 years, was admitted to the Brooklyn Cancer Institute on Oct. 10, 1932 complaining of vaginal bleeding and pain in the left lower abdomen, and the loss of 25 pounds in one year.

The patient was a nullipara. She began to menstruate at the age of 13. Her periods were always regular and lasted three days. Her last normal period was two years previous to admission. Since then she had developed menorrhagia, metrorrhagia, foul leucorrhea and dysparunia. For thirteen days before admission she had bled quite profusely.

Her past history was inconsequential. She had suffered from "rheumatism" for a number of years, had been in an automobile accident, receiving some abrasions

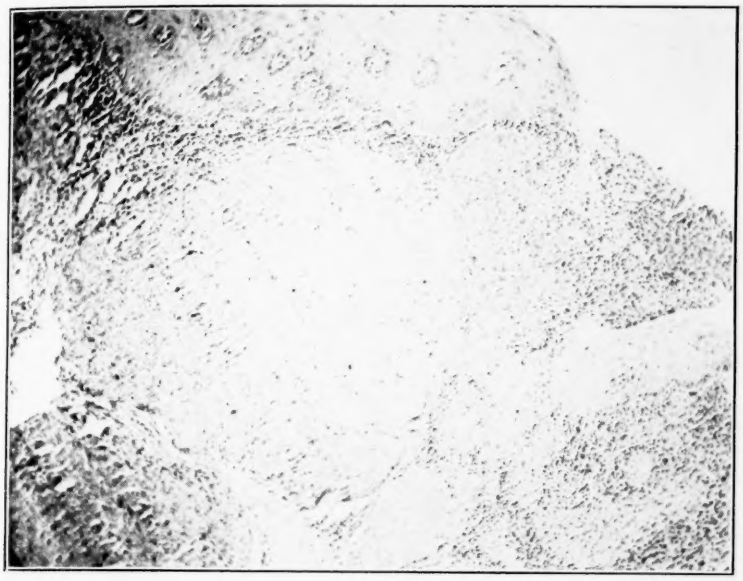

Fig. 1.—Carcinoma of cervix, low power, showing pale neoplastic cells invading the stroma, and leucocytic infiltration.

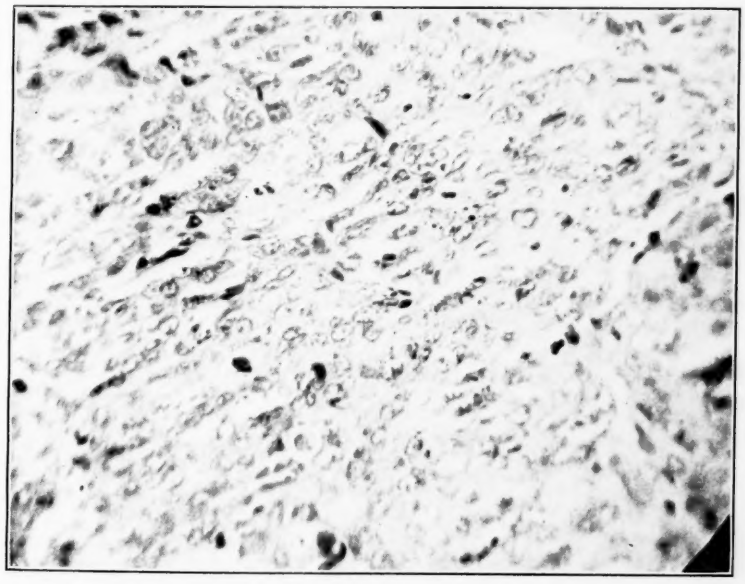

Fig. 2.—Carcinoma of cervix, high power, through neoplastic area showing large pale cells, prominent vesicular nuclei, and scattered mitotic figures.

and lacerations of the hand. Her mother was dead, her father living and well. There was no history of cancer in the family. Her husband was infected with acute gonorrhea at the time of her admission.

Examination revealed a chronically ill, undernourished colored female, weighing 95 pounds, and appearing several years younger than her actual age of 19. Her temperature was 98.2° F., pulse 100, respiration 20, and blood pressure 114/82.

The abdomen was slightly distended, a large firm fixed tumor filled the entire pelvis and extended as far as the umbilicus. Vaginal examination revealed the entire parametrium and cervix fused into one hard, stony mass, continuous with the tumor palpated abdominally. The cervix and parametrium were covered with an ulcerating, sloughing malignant tissue, which could be wiped away with a sponge forceps. The rest of the physical examination did not show anything of note.

The blood Wassermann was four-plus. The blood count was 2,600,000 red cells, 50 per cent hemoglobin, and 18,500 white count. A biopsy from the cervix was reported as anaplastic carcinoma (Figs. 1 and 2).

The patient received x-ray therapy to the pelvis, but became progressively worse. The abdomen became distended with fluid, and she developed edema of the lower extremities. On Jan. 17, 1933, she was transferred to an institution for incurable cancer patients, where she died a week later. Consent for autopsy was not obtained.

REFERENCES

(1) *Bonner, Adolph:* Am. J. Obst. & Gynec. **14:** 175, 1927. (2) *Morse, Arthur H.:* Ibid. **19:** 520, 1930. (3) *Baldwin, L. Grant:* Ibid. **21:** 728, 1931. (4) *Ludwig, D. B.:* Ibid. **31:** 536, 1936.

SPECIFIC URETHRITIS IN A MALE NEWBORN

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GENITAL gonorrhea is a relatively common infection among young children. However, it is extremely rare in the newborn. In fact, I have been unable to discover an instance of gonorrheal urethritis in the male newborn in the available literature. Villen gives an account of six cases of gonorrhea of the genital tract in newborn infants observed in material consisting of 16 boys and 31 girls, born of 47 mothers afflicted with gonorrhea. Of these, 6 girls had a vulvovaginitis with demonstrable gonococci. It is probable that the condition is occasionally overlooked. One author states that the symptoms are not uniform, and their intensity is extremely variable. In some cases the redness, swelling, and discharge are insignificant. In others there are considerable demonstrable findings. The mode of infection is not unanimously agreed upon. Some writers feel that infection occurs later while others admit an intrapartum infection. One might certainly think that breech presentations and premature rupture of the bag of waters with subsequent infection of the amniotic cavity predispose to infection. Hence, because of its rarity, the following case report is submitted.

G. M. C. (Hospital No. 52103) was born to a white primipara, 23 years of age, on Aug. 16, 1938. The mother reported for antepartum care on March 18, 1938. History at that time disclosed no evidence of previous specific infection. Examination revealed a healthy woman who was five months pregnant. Kolmer and Kahn tests were negative. Vaginal smears were negative for gonorrhea. Pelvic measurements were within normal limits. Subsequent antepartum course was uncomplicated. The delivery was spontaneous after a 19-hour labor (second stage 2 hours). Perineum was intact. The baby was a normal male, weighing 8 pounds 2½ ounces. One per cent silver nitrate was instilled in the eyes. The puerperium was afebrile. On the

fourth day postpartum, a discharge from the baby's penis was noted. The baby was isolated and smears were taken. They were positive for gram-negative intracellular diplococci. The following treatment was instituted: Sulfanilamide gr. ½ every four hours and 10 per cent argyrol pack to glans penis four times a day. The baby was breast fed. The mother was isolated and smears taken from the lochial discharge were found to contain gram-negative intracellular diplococci. The mother and the father were both questioned concerning the possible source of the infection, and it was discovered that the husband acquired the disease after the mother had begun her antenatal care and had transmitted it to her late in the pregnancy. She carried the disease unknowingly. Treatment was also instituted in the mother and the disease was eventually arrested. The discharge from the baby's penis subsided rapidly. However, smears were positive for six weeks. Treatment was discontinued after three negative smears were obtained.

Because there are no available reports of a similar instance of urethritis in a male newborn, it is impossible to compare the course of this patient with others. In noting Villen's results in the treatment of newborn female genital infections, one would conclude that the sulfanilamide offers relief more readily.

REFERENCE

Villen, A. F.: Acta dermat.-venereol. **13**: 315, 1932.

807 BROADWAY

Sjovall, A.: The Mucosa of the Cervix Uteri, Acta obst. et gynec. Scandinav. **18:** Supplement 4, 1938.

The author studied the mucosa of the uterine cervix with a view to determining the effect of hormones on it in the nonpregnant state. His material consisted of 99 specimens, of which 60 were obtained at autopsy, and 39 by operative means (12 hysterectomies and 27 cervical biopsies). The material was collected from newborn babies, young girls, mature women, and women past the climacteric.

The author found that in childhood and old age there is no evidence of hormonal action. During the reproductive years there are cyclic changes in the cervical mucosa. Corresponding to the proliferate phase of the endometrium, there is intense proliferation in the cervical mucosa. This proliferative phase is absent shortly before, during, and immediately after the menstrual flow, it reaches its greatest development at the time of ovulation, and accounts for the secretory changes observed in the cervix at that time.

In cases of amenorrhea due to atrophy of the uterine mucosa where there is no hormonal activity, cyclic changes in the cervix are absent. On the other hand, in cases of excessive hormonal action there is excessive proliferation of the cervix epithelium, in all probability caused by estrin.

The author experimentally investigated the effect of hormonal stimulation on the cervix in guinea pigs. He found that the cyclic changes were due to estrin but that progestin may have an inhibitory effect on estrin. He also observed that the passage of spermatozoa readily takes place by means of the motility of the sperm during the estrus phase when proliferation and secretion in the cervix are at their height. On the other hand, the transportation of sperm in this way is practically absent in the nonestrous phase and in castrates. If the estrous phase is reproduced in castrates by the administration of estrin, the possibility of the passage of spermatozoa is restituted.

J. P. GREENHILL.

A SIMPLE TECHNIQUE FOR CRANIOTOMY ON THE HIGH AFTERCOMING HEAD

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WITH a high aftercoming head, such as in cases of hydrocephalus, it may be very difficult or impossible to do a craniotomy through the baby's mouth. The other alternative is through the occiput. However, attempt at direct perforation through the occiput of the high aftercoming head may greatly endanger the mother's soft parts and the bladder.

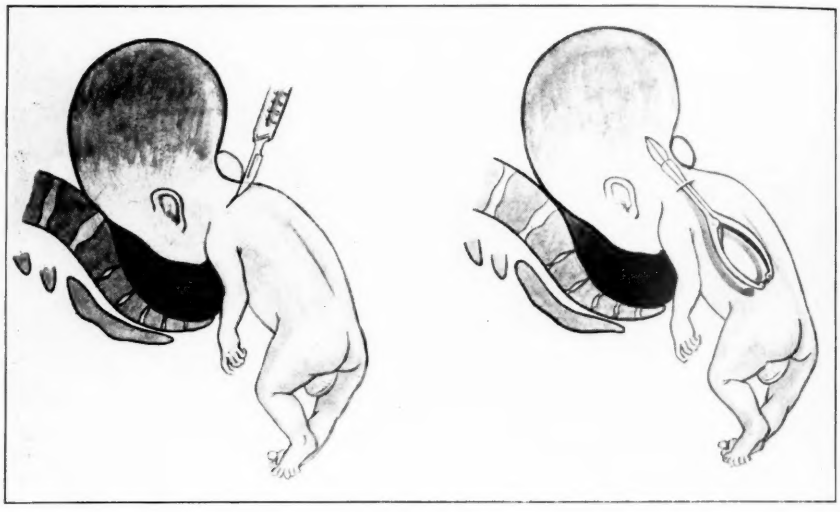

Fig. 1. Fig. 2.

I have found the following technique useful. As illustrated in Fig. 1, a small transverse incision is made through the skin at the base of the neck. Then, as shown in Fig. 2, a Naegele perforator is introduced beneath the skin and tunneled to the suboccipital region. Here the perforation may easily be made into the cranial cavity through the occipital plate, without fear of the perforator glancing off the skull. After the cerebrospinal fluid escapes, there is enough collapse of the skull to make delivery easy.

508 HUME-MANSUR BUILDING

Department of Practical Problems in Obstetrics and Gynecology

CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

DIETARY REQUIREMENTS IN PREGNANCY

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EVIDENCE was presented in a previous paper[1] to show the relationship between the fetal requirements and the maternal diet with respect to some minerals. The facts summarized in that study indicate clearly that certain dietary demands must be met to protect both mother and offspring from clinical pathologic changes during pregnancy. In this review of foods and accessory substances, it is hoped that the important dietary constituents discussed will permit of a nutritional margin sufficient to protect the mother, fetus, and infant even from early changes, subclinical in nature.

Although pregnancy under normal conditions is essentially a physiologic process, it makes special demands on the maternal organism, and diets adequate under ordinary conditions may fail to meet the increased requirements. Barborka,[2] after a study of American diets, concludes that many of our concentrated foods are low in vitamins, residue and alkaline minerals and high in carbohydrates and acid minerals. The foods that correct deficiencies common to our diet are milk, eggs, and leafy vegetables. These protective foods are highly essential during pregnancy and can prevent maternal and fetal morbidity due to demineralization and avitaminosis.

The average increase in weight[3] during pregnancy amounts to 9.7 kilo with a standard deviation of 4.3 kilo. Provided the patient is near the optimum for her height and age when conception occurs, we have for several years attempted to restrict the total weight gain to approximately 7.5 kilo (16.5 pounds) or a maximum weekly gain of 225 gm. (0.5 pound). This increase is equivalent to the weight of the fetus, placenta, amniotic fluid, and the maternal physiologic changes incidental to pregnancy.

The daily caloric intake required during this period varies greatly with the individual. The figures given[4-6] are from 2,000 calories in the early part of pregnancy to 3,500 calories in the last months. If obesity develops, the caloric intake must be reduced without decreasing the necessary minerals and vitamins. Efforts to control the size of the fetus near term by low caloric intake are generally unavailing and may do considerable harm if essential food constituents are withheld. Since the fetus in utero is essentially parasitic and the

growth impulse is satisfied irrespective of the mother's diet, it seems most irrational to starve the mother during the last months of pregnancy in order to obtain a small baby. The correlations between weight of the child and the adequacy of the maternal diet are apparently not disturbed[7] unless the women are extremely undersized or undernourished. In severe malnutrition of the mother leading to osteomalacia (adult rickets), it has been found that the fetus frequently shows marked signs of congenital rickets. There is also evidence indicating that qualitative deficiency of the diet may have a cumulative effect since infants from subsequent pregnancies are more affected than the first-born.

THE FOODS IN PREGNANCY

Carbohydrates.—The carbohydrate metabolism is deranged in normal pregnancy as indicated by the ease with which a glycosuria can be produced and the tendency for the blood sugar curves to be abnormal. Williams[8] found in repeated miscarriages that the blood sugar curve showed a "lag" and that there was often glycosuria but no diabetes mellitus. The use of insulin and a reduction in the carbohydrate intake to 150 or 200 gm. in such cases brought 11 out of 19 pregnancies successfully to term. The possibility of a disturbance in the carbohydrate metabolism as a cause of abortion should be kept in mind, but the very fact that these patients were seen early enough in pregnancy to permit proper supervision, introduces other factors which may have prevented abortion.

The daily intake of carbohydrates according to Shukers and others[4] is 300 to 340 gm., Coons,[5] 336 gm., and Sandiford and others,[6] 149 gm. in the thirteenth week, to 225 gm. in the thirty-eighth to fortieth week. In pregnancy when nausea and vomiting occur, it is advisable[58] to give a high carbohydrate diet every two hours. According to Harding and Potter[9] and other investigators, an abnormal carbohydrate and fat metabolism are factors in causing hyperemesis gravidarum. When severe toxemia of pregnancy is present or imminent, Dieckmann[10] suggests the use of an eclamptic diet which consists of only fruits and sweetened fruit juices.

Protein.—From the studies of Hunscher and others,[11] Wilson,[12] and Macy and Hunscher,[13] the nitrogen requirement during pregnancy for growth of the ovum, the uterus and mammary glands is about 135 to 145 gm. In addition to this special nitrogen requirement, the maternal organism tends to show a nitrogen retention in pregnant women of 200 to 400 gm. The daily protein intake necessary to provide for adequate nitrogen retention is, according to Coons and co-workers,[5, 14, 15] 70 gm., Adair and Dieckmann and others,[17] 75 gm., Sandiford and co-workers,[6] 90 to 100 and other investigators from 100 to 119 gm.[4, 13, 16]

The relation of protein content in the diet to the complication of toxemia in pregnancy, is not altogether clear. Strauss[18] contends that a diet low in protein may be the cause of toxemia in pregnancy. He bases his belief on the fact that his toxemic patients had low values for serum protein and that they were successfully treated by a high protein diet supplemented by vitamin B_1 and liver. On the other hand, it appears that in a small percentage of pregnant women the protein must be rigidly restricted during the latter part of gestation in order to avoid symptoms of toxemia.

From extensive studies of serum proteins, Dieckmann[19] has not been able to substantiate these findings of Strauss. Several hundred patients have had serum protein determinations and only those patients with obvious nephrosis have had a low serum protein. He states that the serum protein concentration in normal pregnancy is 6.4 gm. per cent with a standard deviation of 0.4 gm. per cent, and in pre-eclamptic patients the average is 6.0 gm. per cent; in the vascular renal group, 6.6 gm. per cent; and in eclampsia, 6.7 gm. per cent. Unpublished work by Adair and Dieckmann based on an additional several hundred normal patients who were followed during pregnancy, indicate a serum protein concentration of 6.6 gm. per cent with a standard deviation of 0.4 gm. per cent. Furthermore, Dieckmann reports no improvement in toxemic patients who were placed on a diet containing 100 or more gm. of protein.

Fat.—Fat appears to be of primary importance as a carrier of essential vitamins A, D, E, and F. The optimal amounts in the diet for pregnant women are not known. According to Sandiford and others[6] the daily intake is from 107 to 113 gm., Coons[5] 103 gm., and Shukers and others[4] 112 to 139 gm. Complications in pregnancy directly associated with the intake of fat have not been clearly demonstrated.

Fluids.—Many workers agree that the ingestion of water in pregnancy should be liberal. Coons and others[15] found that the daily intake of water from foods and drinks totaled roughly 2,100 to 3,700 c.c. with the majority around 2,500 c.c. Thus the amount of fluid ingested when compared with the average daily total caloric intake was roughly 1 gm. of water per calorie in the food. We believe that sufficient water should be ingested to ensure a normal urinary output of 1,200 to 1,500 c.c. per twenty-four hours.

THE INORGANIC CONSTITUENTS IN PREGNANCY

The inorganic constituents calcium, phosphorus, magnesium, iron, copper, and iodine, in the following discussion are not necessarily taken up in the order of their importance but rather as a group having to do with ossification, hemoglobin formation and glandular disturbances.

There is conclusive evidence in the literature[20, 21] to show that animals on deficient mineral diets suffer loss of calcium and phosphorus from the body during pregnancy. While it is not to be hoped that equally direct information can be obtained for the mother and infant, yet evidence may be obtained on the fetus.

We have made determinations that show a 20 per cent increase in the calcium and phosphorus content in a seven-month-old fetus whose mother had been on a controlled mineral intake. In comparison it appears probable that all cases of fetal rickets[22, 23] due primarily to mineral deficient diets during pregnancy, would show hypomineralization. With respect to the mother, the first few infants born may not suffer to any extent, but one of us (W. J. D.)[24] has shown that frequent pregnancies and deficient nutrition have a cumulative effect. Apparently the maternal organism will mobilize calcium not only from the so-called reserves but continue until osteomalacia results and even then fetal rickets cannot be prevented. These findings indicate that differences in the degrees of calcification of fetal skeletons exist. Coons and Blunt[25] concluded, from x-ray examinations of bones of normal

infants, that the calcification of the bones was best where the maternal retention of calcium and phosphorus during pregnancy was highest. Toverud[26] found that the extent of calcification of fetal skulls depended upon the calcium content of the maternal diet. In all cases the mothers of infants with soft skulls either had a diet grossly deficient in calcium or had suffered from hyperemesis.

The calcium and phosphorus requirements of the mother in pregnancy are best satisfied by an intake sufficient to produce positive balances. Coons and co-workers[15] report adequate retentions with a mean intake of only 1.4 gm. of calcium and 1.69 gm. of phosphorus in Southern women. This intake, however, was not productive of adequate retentions in Chicago women receiving less sunshine. Toverud[27] found negative balances common in late pregnancy unless the intake of calcium was from 1.6 to 1.8 gm. per day. Dieckmann, basing his statement on balance studies of patients suffering from a calcium and phosphorus deficiency, advised that the diet in pregnancy contain at least 1.5 gm. calcium and 2.0 gm. phosphorus. Unpublished data by Adair and Dieckmann indicate that if the diet is a proper one an average intake of 1.3 gm. calcium and 1.4 gm. phosphorus resulted in a positive balance for almost all patients studied. Certain conditions may affect the optimum retention of calcium and phosphorus such as the percentage utilization of these minerals from the ingested food, the therapeutic administration of vitamin D and the effect of sunlight or irradiation with ultraviolet light.

The ratio of calcium to phosphorus in food is apparently of much less importance than the actual amounts. Coons and others[15] found that on diets containing a calcium-phosphorus ratio from 0.59 to 1.01, average of 0.86, the retention ratio varied from 0.14 to 2.36, average 1.21. These ratios demonstrate a selective power of the organism to retain calcium and phosphorus from the diet.

The foods rich in calcium are milk of animals and leafy vegetables. Apparently the best sources of calcium and phosphorus are milk and cheese. A quart of milk contains approximately 1.2 gm. of calcium and 0.9 gm. phosphorus. The leafy vegetables contain considerable calcium but the presence of oxalates forming insoluble salts lowers the percentage that can be utilized. "Apparently all other foods fall below the nutritive requirements of man and animals in calcium. Both McCollum and Sherman believe that the average American diet tends to be low in calcium and over-rich in phosphorus. The body is very sensitive to deprivation of calcium in the food and serious damage results to the bony structure and doubtless to other tissue if the diet does not contain sufficient amounts of this mineral."[28]

It is apparent that at least one quart of milk daily is necessary to bring the calcium intake up to the required limits. As substitutes it would take approximately 5 ounces of cheese or 12 average size oranges to have the same calcium content. Calcium salts, whether in the form of gluconate, lactate, or perhaps the best, dicalcium phosphate, are more expensive than milk and are usually excreted almost quantitatively in the urine and feces. It would require some 8 gm. daily of dicalcium phosphate,[29] because of the uncertainty of utilization, to equal the amount obtained from 1 quart of milk.

Apparently when foods containing sufficient calcium and phosphorus are ingested in pregnancy the magnesium requirement is also satisfied.

Coons and others[15] found that a daily intake of 0.35 to 0.45 gm. of magnesium was sufficient to give positive balances in the latter part of pregnancy.

The studies on iron metabolism in pregnancy reported in an earlier paper[1] indicate depletion of maternal stores with successive births. It has been shown that infant's hemoglobin values are normal at birth even where the mother's hemoglobin was low in pregnancy, but that the infant is more likely to develop a hypochromic anemia during the first year. Dieckmann and Adair have a number of cases where the cord blood hemoglobin and cell volume were well below normal if the mother had an anemia. Coons[5, 30] found that an average maternal intake of 15 mg. of iron a day permitted an average retention of 3.2 mg., sufficient to provide for the calculated needs of the mother and fetus. Studies of Adair and Dieckmann and others[17] confirm this work. Macy and Hunscher[13] found that 20 mg. of iron daily was the desirable amount in pregnancy. Apparently the larger amount gives a margin of safety since the availability of iron in different foodstuffs varies and absorption may be dependent upon gastric acidity. The foods rich in assimilable iron are liver, kidney, gizzards, red meats, raisins, prunes, apricots, and peaches. Iron salts and the vitamin B complex may be used to supplement the maternal diet, but their value is very questionable. Where the anemia is marked, transfusions of blood are indicated. In macrocytic anemia the necessity is not for minerals but Castle's extrinsic factor.

Information is very meager on the need of copper in pregnancy. From the studies of Sheldon[31] and Tompsett and Anderson,[32] it was found that the copper content of the blood was increased in pregnancy. Although copper deficiency may not occur frequently, the possibility is indicated since iron and copper together[33] are sometimes necessary to cure anemia when iron alone fails.

In certain sections of the country, where goiter is endemic, the iodine content of the diet must be considered. The amount of iodine needed in pregnancy may best be supplied by the routine use of iodized salt and seafoods, especially cod liver oil. These may be supplemented in special cases by calcium salts of iodized fatty acids.

THE VITAMINS IN PREGNANCY

The requirements for all vitamins appear to be increased in pregnancy. The most important to be discussed are vitamins A, B_1, B_2, C, D, and E.

With respect to vitamin A there is some work which would seem to indicate that the mucous membranes are made more resistant to infection when sufficient quantities of this vitamin are supplied. Maxwell[34] observed an infant born with keratomalacia which, he thought, was caused by the lack of vitamin A in the mother's diet.

The daily amount of vitamin A recommended for pregnant women is 9,000 international units. The richest diets provide scarcely 3,000 units. It may, therefore, be necessary to supplement the diets with the precursor carotene or fish oils high in vitamin A.

With respect to pregnancy, the interest in the fractions of the B complex is in B_1, thiamin, the antineuritic factor and the B_2 complex. In animals, vitamin B_1 deficiency results in failure of conception, resorption of the fetus and frequent abortion and early death from a disorder closely resembling polyneuritis. Polyneuritis may occur,

whatever the previous condition or diet, if there is severe vomiting of pregnancy.[35, 36] In districts where pellagra is prevalent, the increased need of vitamin B_2 complex in pregnancy may unmask the latent disease. If pellagra occurs, an ample amount of vitamin B_2 (riboflavin), the P-P factor and nicotinic acid should be administered.

The food sources of the vitamin B complex are yeast, whole grain breads and oils, cabbage and carrots, leafy vegetables, egg yolk and oysters. To supplement these foods there are a number of concentrated vitamin B complex extracts besides the isolated vitamin B fractions available.

The importance of vitamin C, ascorbic acid, in pregnancy is not well defined. Apparently its deficiency interferes with normal ovulation and conception. Determinations of excretion of vitamin C in human urine indicate that the demand is increased in pregnancy. An ample supply is necessary for protection of the fetus and infant. The daily maternal intake recommended is approximately 75 mg. or 1,500 international units. The foods rich in this vitamin are citrus fruits, tomato, parsley, green or red peppers, uncooked cabbage and other leafy vegetables.

The administration of vitamin D, calciferol, in pregnancy is not a routine procedure in obstetric practice. However, the giving of therapeutic doses of vitamin D as found in cod liver oil and in concentrates, or exposure to sunlight is a most justifiable measure. Careful search of the literature seems to indicate that in the infant a correlation may exist between calcium deficiency, premature births, imperfect calcification, and birth trauma.

It may be said of the premature infant that, in spite of smaller size and easier head molding, birth is more hazardous. It is a known fact that intracranial hemorrhage occurs more frequently than in the full-term infant, probably primarily due to the softness of skull bones. The process of molding, however, does not depend on the softness of the skull bones but on the extent of overriding. It would appear then that firmness of the flat bones in the full-term infant protects the soft brain tissue and that good ossification is to be desired. Abel[37] observed, however, that administration of vitamin D tended to prolong the average duration of pregnancy in the human being about ten days. Along this line Toverud[27] made the interesting observation that on ample diets and vitamin D, except in June, July, and August, a lowering of the incidence of prematurity resulted.

It should be emphasized again that supplementing the diet of the mother with therapeutic doses of vitamin D from fish oils, concentrates or from the action of sunlight on the skin does not permit a decrease in the daily optimum calcium and phosphorus intake. Pregnant women should be given a teaspoonful of good grade cod liver oil, 350 to 400 international units, daily or the gradual exposure to sunlight or irradiation with ultraviolet light sufficient to maintain a slight tan.

Vitamin E, alpha tocopherol, appears to be of most importance in pregnant women subject to habitual abortion. Vogt-Møller[38] successfully brought 17 out of 20 such women to term by giving 40 drops of a vitamin E preparation, wheat germ oil, called "fertilan" thrice daily from the third to the seventh month and thereafter a dessertspoonful of wheat germ thrice daily. Subsequent vitamin E therapy[39] of 52 women suffering from habitual abortion resulted in 38 full-term living infants. Krohn and others[40] and Watson and Tew[41] report successful results in 75 per cent of women suffering from habitual and threatened abortion.

Besides the preparation of vitamin E mentioned, many potent concentrates are on the market. In its natural state, E is found mostly in whole grains, egg yolk, green vegetables, and muscle meat.

Mattill[42] concludes an article on vitamin E as follows:

"More clinical evidence, obtained under carefully controlled conditions, is greatly needed to establish the usefulness of vitamin E therapy in abnormal human reproduction. Until this is at hand, attempts to produce a market for wheat germ oil among prospective parents generally are to be deprecated; so also is the suggested threat of national dietary sterility, *in view of the widespread distribution of vitamin E in the foods belonging in a well-balanced diet.* Individual cases of inadequacy, due perhaps to a faulty absorption or metabolism will not be understood until more is known about the chemistry and physiology of vitamin E."

Vitamin K is of no value to the pregnant or lactating woman but has been used in conjunction with bile salts in the treatment of a few cases of hemorrhagic disease of the newborn.[43]

The difficulty in determining the value in human beings of diets adequate in both food and vitamin content is illustrated by the following reports. Ross, Perlzweig, and co-workers[44] studied a group of pregnant women in an institution. One series for economic reasons received the general diet which was low in milk, butter, eggs, meat, fish, and fresh fruits. Another series had a well-balanced diet with adequate amounts of vitamins A, B complex, D, and E, as well as calcium, phosphorus, and iron. They concluded that there was no significant difference between the two series as to the incidence of toxemia or concentration of hemoglobin and serum protein.

A different aspect is given by the preliminary report of the British Minister of Health[45] who stated that among 4,446 mothers receiving special food, the puerperal death rate was 0.45; the maternal death rate from associated causes, 0.67; and the infant death rate (stillbirth and neonatal), 54. Among 9,040 mothers not receiving special foods, the corresponding rates were 3.54, 1.33, and 83, respectively.*

THE FOODS IN LACTATION

The production of milk in the lactating mother does not require any expenditure of energy other than that contained in the milk itself, which in the human amounts to 700 calories per 1,000 c.c. Restricted muscular activity, freedom from worries, sufficient sleep, and an adequate diet promote milk secretion. However, the energy intake during lactation is materially increased over that in pregnancy. Studies[4, 46, 47] on the caloric requirements of lactating women indicate that 40 to 50 per cent of the total caloric intake may reappear in the milk.

An interesting point stressed by Garry and Stiven[48] in their excellent review is the fact that, "In farm stock it is well known that extra feeding beyond maintenance allowance during the last stage of pregnancy does not appear to affect the birth weight or subsequent growth of young animals, but has a very marked effect on milk yield." Along this line

*Medical Research Council report to the Minister of Health: It is the opinion of the Committee that the results of the analysis of the present experiment should be awaited before further experimental observations are embarked upon. The Committee fear, however, that the practical difficulties in the way of securing precise comparability between the contrasted groups, having regard to the number of possibly relevant factors (age, parity, diet, medical supervision, etc.) are so great that it is unlikely that scientifically adequate conclusions would be reached.

Coons and Blunt[25] found that the greater the nitrogen retention, especially in the last stage of pregnancy, the more likely is lactation to be adequate.

From balance studies during lactation, conclusive evidence is presented in the literature to indicate that all foods are needed in more abundance. The specific effect on milk production by any one food is not easily determined in each instance. However, the ingestion of foods rich in carbohydrates does not appear to augment the yield of milk[49, 50] but tends to increase the fat content. The intake of foods rich in fat increased slightly the volume of milk with considerable increase in the concentration of fats.[4, 50] Deem[50] found that a high protein diet enriched by vitamin B increased the milk yield. Adair[59] stated that a high protein, balanced diet gave maximum milk production. Hunscher et al.[16] observed that subjects on high protein diets during pregnancy with daily nitrogen retentions of 3 gm., had later, during lactation, very high yields of milk. While quality in all three foods may be important, emphasis with respect to proteins is placed especially on dairy products.

The restriction of fluid intake may limit milk yield when all other necessary constituents are supplied in ample amounts. Macy and others[51] found that, beyond certain limits, the amount of liquid ingested by women did not affect milk yield.

The source of supply of minerals for lactating women is a good mixed diet containing one quart of milk daily. At the height of lactation as shown by a number of investigators,[52, 53] it may be difficult on this diet to procure a positive calcium balance. Apparently the daily calcium intake must be four times that present in the secreted milk to prevent body loss.[47] This ratio may be reduced by addition of cod liver oil and yeast to the mother's diet.[54] With respect to the minerals iron, copper, and manganese, many workers agree[55] that addition of these elements to the diet will not increase their concentrations in the mother's milk.

All the vitamins considered necessary in pregnancy are also of importance during the period of lactation, with special emphasis on an adequate amount of the B complex. However, an indiscriminate enrichment of the diet with vitamin concentrates is not advocated. The emphasis should be on the ingestion of mixed foodstuffs containing the natural source of the various vitamins.

As far as is known the concentrations of the various vitamins in the breast milk is largely dependent upon the vitamin content of the maternal diet. The vitamins that may more directly be connected with milk flow are B_1 and E.

There are considerable variations in the amount of foods and vitamins advocated by various investigators for the pregnant woman. We have attempted to list in Table I what we consider are the minimum requirements for the pregnant and lactating woman. If the patient is able to obtain a properly balanced diet containing milk, butter, eggs, meat, fruits, and vegetables, we do not prescribe any vitamins. It is not so much the actual amount of protein, calcium, phosphorus, iron, iodine, etc., in the diet as their assimilability by the patient. We have included the composition of milk, because it forms the basis of all diets requiring large amounts of calcium and phosphorus. Skimmed or better buttermilk may be used to decrease the fat content and thus reduce the caloric value.

TABLE I. THE AVERAGE DAILY HUMAN REQUIREMENT IN PREGNANCY AND LACTATION BASED ON VARIOUS REPORTS

	MILK—1,000 C.C. OR 1 QT.	1-27 WK.	28-40 WK.	LACTATION
Protein	33.0 gm.	60.0 gm.	80.0 gm.	90.0 gm.
Fat	40.0 gm.	70.0 gm.	70.0 gm.	100.0 gm.
Carbohydrate	50.0 gm.	350.0 gm.	400.0 gm.	435.0 gm.
Calories	690.0	2,300.0	2,600.0	3,000.0
Calcium	1.2 gm.	0.7 gm.	1.4 gm.	1.4 gm.
Phosphorus	0.9 gm.	1.3 gm.	1.6 gm.	1.6 gm.
Magnesium	0.12 gm.	0.3 gm.	0.45 gm.	0.45 gm.
Iron	Liver, muscle, grapes	0.020 gm.	0.020 gm.	0.015 gm.
Iodine	Cod-liver oil	Iodized	Table	Salt
Vitamin				
A	Halibut liver oil	4,000.0 U.S.P.	9,000.0 U.S.P.	9,000.0 U.S.P.
B_1	Yeast, whole grains	0.4 mg.— 200 I.U.	0.8 mg.— 400 I.U.	600.0 I.U.
B_2	Yeast, whole grains, liver	1.5 mg.— 600 I.U.	3.0 mg.—1,200 I.U.	3.0 gm.—1,200 I.U.
C	Citrus fruits, vegetables	20.0 mg.— 400 I.U.	75.0 mg.—1,500 I.U.	75.0 mg.—1,500 I.U.
D	Fish liver oil, egg yolk	300.0 U.S.P.	800.0 U.S.P.	800.0 U.S.P.
E	Whole grains, lettuce	?	?	?

4 c.c. cod liver oil = approximately 3,000 units A and 300 units D.
40 c.c. orange juice = approximately 400 units C.

SUMMARY

Studies of the maternal diets in pregnancy and in lactation indicate that inadequate diets inevitably affect the well-being of the mother, fetus, and infant. Although deficiencies in diet causing morbidity of the fetus, such as rickets, hypoplasia of the teeth,[56] tetany[57] and anemia, may be corrected in early infancy, yet the first opportunity has been lost in not preventing the condition before it had a chance to develop. To correct these disorders of the fetus, emphasis should be placed on the proper maternal diet during the last trimester, provided that the mother has previously been in a good state of nutrition. It is interesting to note, however, that the production of an adequate supply of milk is dependent upon an optimum diet during the last trimester of pregnancy. The one important fact to be emphasized is that supplements of manufactured concentrates cannot be substituted for natural foodstuffs. In this day and age, when transportation of natural foodstuffs offers scarcely any problem, there should be no need for dietary disturbances in certain sections of this country due either to lack of food, vitamins, or to essential minerals.

REFERENCES

(1) *Swanson, W. W., and Iob, V.:* Am. J. Obst. & Gynec. **38:** 382, 1939. (2) *Barborka, C. J.:* Med. Clin. North America **15:** 139, 1931. (3) *Dieckmann, Wm. J., and Brown, I.:* Am. J. Obst. & Gynec. **38:** 214, 1939. (4) *Shukers, C. F., Macy, I. G., Donelson, E., Nims, B., and Hunscher, H. A.:* J. Nutrition **4:** 399, 1931. (5) *Coons, C. M.:* J. Am. Diet. Assn. **9:** 95, 1933. (6) *Sandiford, I., Wheeler, J., and Boothby, M. W.:* Am. J. Physiol. **96:** 191, 1931. (7) *Wardlaw, H. S. H., and Dart, E. E. P.:* Med. J. Australia **2:** 377, 1934. (8) *Williams, E. C. P.:* Lancet **225:** 858, 1933. (9) *Harding, V. J., and Potter, C. T.:* Brit. J. Exper. Path. **4:** 105, 1923. (10) *Dieckmann, Wm. J.:* Surg. Gynec. Obst. **59:** 678, 1934. (11) *Hunscher, H. A., Donelson, E., Nims, B., Kenyon, F., and Macy, I. G.:* J. Biol. Chem. **99:** 507, 1932-33. (12) *Wilson, K. M.:* Bull. Johns Hopkins Hosp. **27:** 121, 1916. (13) *Macy, I. G., and Hunscher, H. A.:* Am. J. Obst. & Gynec. **27:** 878, 1934. (14) *Coons, C. M., and Marshall, G. B.:* J. Nutrition **7:** 67, 1934. (15) *Coons, C. M., Schielfelbush, A. J., Marshal, G. B., and Coons, R. R.:* Oklahoma Agric. Mech. Coll., Agric. Exper. Station Bull. No. 22, 1935. (16) *Hunscher, H. A., Cope, F., Sternberger, H. R., Erickson, B. M., and Macy, I. G.:* J. Nutrition **9:** 1935, No. 6, Suppl. p. 13. (17) *Adair, F. L., Dieckmann, Wm. J., Michel, H., Arthur, B., Costin, M., Campbell, A., Dunkel, F., Kramer, S., and Lorang, E.:* Unpublished data. (18) *Strauss, M. B.:* J. Clin. Investigation **14:** 710, 1935. (19) *Dieckmann, Wm. J.:* Am. J. Obst. & Gynec. **26:** 543, 1933. (20) *Sherman, H. C., and MacLeod, F. L.:* J. Biol. Chem. **64:** 429, 1925. (21) *Toverud, K. U., and Toverud, G.:* Skandinav. Arch. f. Physiol. **55:** 282, 1929. (22) *Maxwell, J. P., Hu, C. H., and Turnbull, H. M.:* J. Path. & Bact. **35:** 419, 1932. (23) *Rector, J. M.:* J. Pediat. **6:** 161, 1935. (24) *Dieckmann, Wm. J.:* Am. J. Obst. & Gynec. **23:** 478, 1932. (25) *Coons, C. M., and Blunt, K.:* J. Biol. Chem. **86:** 1, 1930. (26) *Toverud, K. U.:* Acta Paediat. **12:** 267, 1931-32. (27) *Toverud, K. U.:* Hospitals tidende **77:** 1934, No. 15, Proc. 1, quoted from Nutrition Abstr. & Rev. **5:** 855, 1935-36. (28) White House Conference, Report of the Committee on Milk Production and Control, **IIC,** 226, 1932. (29) *Boyd, J. D.:* J. Pediat. **8:** 234, 1936. (30) *Coons, C. M.:* J. Biol. Chem. **97:** 215, 1932. (31) *Sheldon, J. H.:* Brit. M. J. **2:** 869, 1932. (32) *Tompsett, S. L., and Anderson, D. F.:* Brit. J. Exper. Path. **16:** 67, 1935. (33) *Irving, F. R.:* Am. J. Obst. & Gynec. **29:** 859, 1935. (34) *Maxwell, J. P.:* J. Obst. & Gynaec. Brit. Emp. **39:** 764, 1932. (35) *Plass, E. D., and Mengert, W. F.:* J. A. M. A. **101:** 2020, 1933. (36) *Wegner, C.:* Trans. Am. Gynec. Soc. **63:** 199, 1938. (37) *Abel, K.:* Ztschr. Ernährung **1:** 366, 1931. (38) *Vogt-Møller, P.:* Acta Obst. et Gynec. scandinav. **13:** 219, 1933. (39) *Vogt-Møller, P.:* Ugesk. f. laeger **99:** 625, 1937. (40) *Krohn, L., Falls, F. H., and Lackner, J. E.:* Am. J. Obst. & Gynec. **29:** 198, 1935. (41) *Watson, E. M., and Tew, W. P.:* Ibid. **31:** 352, 1936. (42) *Mattill, H. A.:* J. A. M. A. **110:** 1831, 1938. (43) *Waddell, W., Guerry, D., Bray, W., and Kelley, O.:* Proc. Soc. Exper. Biol. & Med. **40:** 432, 1939. (44) *Ross, R., Perlzweig, W., Taylor, H., McBryde, A., Yates, A.,*

and Kondritzer, A.: Am. J. Obst. & Gynec. **35:** 426, 1938. (45) Minister of Health, J. Royal Inst. Public Health & Hyg. **1:** 572, 1938. (46) *Hoobler, B. R.:* Am. J. Dis. Child. **14:** 105, 1917. (47) *Shukers, C. F., Macy, I. G., Donelson, E., Nims, B., Hunscher, H. A.:* J. Am. Diet. Assn. **7:** 235, 1931. (48) *Garry, R. C., and Stiven, D.:* Nutrition Abst. & Rev. **5:** 855, 1935-36. (49) *Shukers, C. F., Macy, I. G., Nims, B., Donelson, E., and Hunscher, H. A.:* J. Nutrition **5:** 127, 1932. (50) *Deem, H. E.:* Arch. Dis. Childhood **6:** 53, 1931. (51) *Macy, I. G., Hunscher, H. A., Donelson, E., and Nims, B.:* Am. J. Dis. Child. **39:** 1186, 1930. (52) *Donelson, E., Nims, B., Hunscher, H. A., and Macy, I. G.:* J. Biol. Chem. **91:** 675, 1931. (53) *Hunscher, H. A.:* J. Biol. Chem. **86:** 37, 1930. (54) *Macy, I. G., Hunscher, H. A., McCosh, S. S., and Nims, B.:* J. Biol. Chem. **86:** 59, 1930. (55) *Elvehjem, C. A., Herrin, R. C., and Hart, E. B.:* J. Biol. Chem. **71:** 255, 1926-27; *Kemmerer, A. R., and Todd, W. R.:* J. Biol. Chem. **94:** 317, 1931; *Mackay, H. M. M.:* Med. Res. Counc. Spec. Rep. Series, London, 157, 1931; *McGowan, J. P., and Crichton, A.:* Biochem. J. **17:** 204, 1923; Ibid. **18:** 265, 1924; *Zondek, S. G., and Bandmann, M.:* Klin. Wchnschr. **10:** 1528, 1931. (56) *Wolfe, J. J.:* Am. J. Dis. Child. **49:** 905, 1935. (57) *Snelling, C. E., and Brown, A. J.:* J. Pediat. **10:** 167, 1937. (58) *Dieckmann, Wm. J., and Crossen, R.:* Am. J. Obst. & Gynec. **14:** 3, 1927. (59) *Adair, F. L.:* Ibid. **9:** 1, 1925.

Grodberg and Carey: Sulfanilamide in the Treatment of Gonorrhea in the Female, New England J. M. **218:** 1092, 1938.

All of the patients included in this study were treated with sulfanilamide, the average daily dose being from 20 to 30 gr. for a four- to six-week period.

In every case they demonstrated the gonococcus intracellularly in smears of the exudate stained by Gram's method.

This treatment was the only one utilized, and the patients were told not to take medicated douches except in special cases. Originally these patients were seen three times a week, but later at weekly visits. They were advised to refrain from coitus and the use of alcohol.

The type cases have been acute endocervicitis, acute urethritis, vulvovaginitis, both adult and juvenile types, and acute pelvic inflammatory disease. The authors treated a few patients in various stages of pregnancy.

In less than one week, usually about three to four days, there was subjective improvement. The smears taken at about one week after the onset of medication showed fewer gonococci, with the organisms situated extracellularly.

The purulent nature of the smear continued, but in from seven to ten days gonococci were absent. Acute masses, both tubo-ovarian and vulvovaginal, resolve in about ten to fourteen days.

The drug was ineffective in the majority of cases of infantile vulvovaginitis, utilizing both topical and oral sulfanilamide medication. There were 85 per cent cures in the authors' adult group.

All observers report a lower percentage of cures in women.

J. P. Greenhill.

Alexin and Herrnberger: Investigation of the Vaginal Content of Newborn and Nursing Babies, Zentralbl. f. Gynäk. **62:** 9, 1938.

The writers found that characteristic changes in the vagina of newborn babies occurred during the first few weeks of life. In the first week vaginal smears revealed the top layer of cells of the vaginal mucosa. During the second week the cornified cells disappear and cells from the deeper layers appear.

On the second and third days bacteria and leucocytes are found. The latter disappear when the cornified cells make their appearance and they return when the cells of the deeper layers are found in the smears. The bacterial flora consists of Döderlein bacilli until the middle of the second week after which there is a mixed coccal flora.

J. P. Greenhill.

Editorial

The Prevention of Syphilis in Marriage

IN THE hope of reducing the incidence of marital and congenital syphilis, several states have included in their statutes specific laws calling for compulsory serologic tests before contemplated marriage and during pregnancy. These laws have been in force too short a time to make possible any evaluation of their efficacy or of their general public approval. However, it is of interest to note that records now available show a definite trend in their acceptance.

Sixteen states now have premarital examination laws, according to *Health News*, the official organ of the New York State Department of Health, and in six states every pregnant woman must have a serologic test for syphilis at the time of the first medical examination. The former are made ineffectual to some degree by couples who marry outside of these states but steps are being taken to void this. Surveys in six states suggest that marriages at first undergo a decrease but this is only temporary and evidently, after the purpose of the law is understood and appreciated, there is no reduction in the usual rate. In five states in which premarital tests were studied, the reactions were positive in 1.3 per cent.

The experience of New York State, exclusive of New York City, with tests in early pregnancy is of interest. During a nine months' period, 188 cases of syphilis were discovered among expectant mothers. As near as can be determined from laboratory records, the incidence of positive tests was 1.8 per cent. One-half of the mothers found to have syphilis were under 28 years of age and only one-fourth of the tests were made before the fifth month.

Obviously the introduction of this legal protective measure against the transmission of congenital syphilis is of value in case finding and, as time goes on, it will become recognized as an important and effective public health measure. A more universal adoption throughout the country of similar laws seems necessary to develop more satisfactorily the attack against this debilitating disease, which constitutes only a part of the larger movement to root out one of the most serious plagues of mankind. The obstetrician has an important function to perform and he need no longer hesitate to employ the necessary serologic tests as a part of the routine prenatal examination, for the public is rapidly acknowledging the desirability of such measures for its protection.

In the medical profession, however, there is by no means an unanimity of opinion in favor of the legislation as so many factors are involved. Snow[1] has recently declared himself in the affirmative; Nelson[2] the negative. Stokes and Ingraham[3] have given a lengthy discussion without assuming a positive or negative opinion, while Kolmer,[4] after a thorough

[1] *Snow, W. F.:* Am. J. Syph., Gonorr. & Ven. Dis. **23**: 277, 1939.
[2] *Nelson, N. Q.:* Am. J. Syph., Gonorr. & Ven. Dis. **23**: 288, 1939.
[3] *Stokes, J. H., and Ingraham, N. R.:* J. A. M. A. **112**: 1133, 1939.
[4] *Kolmer, J. A.:* J. A. M. A. **112**: 2385, 1939.

discussion of reasons for and against legally required premarital and pregnancy blood tests, finds himself in favor of premarital examinations, including blood tests, and certainly in favor of blood tests during pregnancy or at delivery when conducted by methods possessing the maximum of sensitivity consistent with specificity and by serologists of skill and experience. He gives the following ten reasons in *favor* of such legally required *premarital* examinations:

1. Because marriage inevitably involves syphilitic men and women in view of the high incidence of the disease.

2. Because they will tend to lower the incidence of syphilis.

3. Because they are the most valuable single means for the detection of the disease, especially after the primary, or chancre, stage.

4. Because of the inadequacy or absence of a history of infection.

5. Because of the inadequacy of clinical detection of the disease.

6. Because they will reduce the incidence of syphilis to spouse and children.

7. Because they will reduce the incidence of the economic hazards of marriage from incapacity or early death of the spouse.

8. Because they will reduce the incidence of divorce.

9. Because they will greatly encourage the thorough treatment of syphilis.

10. Because they are an excellent phase of the educational program against syphilis.

Four reasons are offered, however, *against* legally required *premarital* examinations as follows:

1. Because premarital blood tests may give nonspecific or falsely positive reactions.

2. Because positive blood reactions as the only evidence of syphilis may not always indicate a danger to marriage, especially in the case of thoroughly treated chronic syphilis.

3. Because they may discourage marriage and promote sexual promiscuity.

4. Because premarital blood tests alone may not detect syphilis, especially in its incubationary and primary stages.

Five reasons are given in *favor* of blood tests during *pregnancy or at delivery* as follows:

1. Because they afford an excellent opportunity for detecting syphilis in both married and unmarried women.

2. Because the detection and treatment of syphilis in pregnancy increases the chance of the birth of a nonsyphilitic child, with a reduction in the number of miscarriages and in infant mortality.

3. Because the detection of syphilis in pregnancy results in the treatment of the mother, especially during subsequent pregnancies.

4. Because the detection of syphilis in pregnancy may result in its detection and treatment in the child after birth.

5. Because the detection of syphilis during pregnancy may lead to its detection and treatment of the father and other children.

Kolmer knows of no valid or important reasons *against* the legal requirement of blood tests during pregnancy or at delivery. Falsely positive reactions are no more likely to occur than in the case of men and nonpregnant women with acceptable methods skillfully conducted. It is true that difficult situations may be created in the case of syphilitic husbands infecting their wives without the knowledge of the latter but, after all, no physician should be a party to any arrangement that leaves an unsuspecting wife to her fate. It is also true that women objecting to blood tests during pregnancy may elect to be delivered by a midwife or neglect calling a physician until in labor. For these reasons, Kolmer believes that the results of a blood test during pregnancy or at delivery should be required to be reported on all birth certificates.

Heaton, Claude Edwin: Prenatal Care, M. Clin. North America, November, 1937, p. 1859.

Prenatal care implies constant and efficient supervision with hospitalization for those conditions too serious to be adequately coped with at home. The diagnosis and management of intercurrent or associated conditions complicated by pregnancy necessitate individualization and the aid of internal medicine. Nutritional aspects of pregnancy deserve consideration in the prevention of deficiency states and congenital syphilis is a preventable disease. An effort should be made to prevent eclampsia by prompt attention to signs of hypertensive vascular disease evidenced by a progressive rise of the diastolic blood pressure, proteinuria, upset water balance and spastic changes in the retinal arterioles. Ante-partum bleeding necessitates ruling out placenta previa. Fetal malposition, especially breech presentation, should be corrected where possible. The relative size of the birth canal and passenger should be determined in advance for possible disproportion and for this purpose roentgenography should be utilized.

J. P. GREENHILL.

Young, H. H.: Diverticulum of the Female Urethra, South. M. J. 31: 1043, 1938.

There are a case report, a review of the literature, and a brief discussion of this anomaly.

In a 57-year-old multipara who presented a history of painful, frequent urination with difficulty in starting the stream, a rounded elastic mass 3 cm. in diameter was found projecting into the vagina from behind the urethra. Cystoscopic examination revealed an entirely normal bladder. In the floor of the urethra, however, there was noted a small opening which led into a periurethral pouch of a diameter of approximately 2½ cm. The relations of this structure to the bladder were demonstrated by cystourethrogram. Surgical removal was successfully accomplished by transverse incision in the vaginal mucosa, dissection of the pouch, and transverse closure of the defect in the floor of the urethra by continuous suture. Patient was relieved of her symptoms.

True congenital diverticuli of the female urethra are rare, and usually occur in the median portion of the urethra. Their etiology has not been definitely established, but the possible causal relationship to Müllerian and Gärtner duct remnants has been mentioned. Despite the fact that urethral glands are not commonly found at the usual site of the development of the diverticuli, etiologic importance has been claimed for them by some writers.

In the absence of complications such as suppuration, calculus formation, or mechanical interference with urination or coitus, there may be few symptoms. It is suggested that in some cases the condition is overlooked or incorrectly diagnosed as cystocele.

ARNOLD GOLDBERGER.

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Gynecology

For the first time both the investigator and the clinician have at their disposal a monograph which covers the physiology of the uterine muscle.[1] The author has contributed much to our knowledge by his personal investigations, and in addition has carefully assembled a continuous exposition of all that has been gained from the work of other physiologists.

The clinician and the obstetrician will find many of the basic causes which produce sterility, abortion, or other disturbances of pregnancy, and explanations of some of the other manifestations of functional disturbances of the female genital tract.

Even if the reader does not desire to read this book from cover to cover, he will be able to refer to it in connection with various problems which constantly confront the investigator and the clinician.

—*R. T. Frank.*

Witherspoon has written a *Clinical Pathological Gynecology*,[2] in which he correlates the gross and microscopic pathology with clinical interpretation of the etiology, symptoms, diagnosis, treatment, and prognosis of each condition. This should prove of value to medical students, particularly as the combined viewpoint emphasizes the importance of gross and microscopic pathology in connection with clinical knowledge. The text is short, very up to date and while it contributes nothing essentially new, the presentation is good. The numerous illustrations, 271 in number, make this a very useful book for teaching purposes. While the microphotographs are practically all original, the large number of the gross pictures are from well-known sources which are duly credited. The book will prove of great service to teachers, particularly those whose clinical material and experience are limited, in preparing an excellent course for students. The reproduction of illustrations and bookmaking are faultless.

—*R. T. Frank.*

After a lapse of two years Weibel offers the gynecologic volume of his *Lehrbuch der Frauenheilkunde*[3] which completes his presentation of the subject. In this second volume, which deals mostly with gynecology, he develops more fully the physiology of the female pelvic organs in considering the various alterations and dysfunctions. In a logical manner the text carries through tumor formations, displacements, inflammations, and the relationship of the genital organs to the surrounding

[1] **Physiology of the Uterus.** With Clinical Correlations. By Samuel R. M. Reynolds, Fellow, John Simon Guggenheim Memorial Foundation, University of Rochester School of Medicine and Dentistry, Associate Professor of Physiology, Long Island College of Medicine, Brooklyn, N. Y. Illustrated, 447 pages. Paul B. Hoeber, Inc., 1939.

[2] **Clinical Pathological Gynecology.** By J. Thornwell Witherspoon, Formerly Associate Professor of Experimental and Pathological Gynecology, Indiana University Medical Center, Indianapolis. Illustrated with 271 engravings, 400 pages. Lea & Febiger, Philadelphia, 1939.

[3] **Lehrbuch der Frauenheilkunde,** in zwei Bänden. Von Prof. Dr. W. Weibel, Vorstand der II, Universitäts-Frauenklinik in Wien. Zweiter Band: Gynäkologie. Urban & Schwarzenberg, Berlin und Wien, 1939.

structures and other bodily systems. After portraying various diagnostic methods, the subject of radiation is fully considered, and there is a chapter on other physical methods. Typical operative procedures are described, and there is a short discussion of the relationship of vitamins to pelvic physiology, and a section regarding the sedimentation time in pelvic diseases.

Weibel emphasizes the psychic aspects of adolescence and the menopause, and cautions against too great a reliance on hormones to control symptoms of the latter phase. Abnormal constitutional types and tendencies are succinctly described, and Weibel very cleverly correlates their effect upon the genital apparatus as well as their relation to pelvic deficiencies. The diagnoses of developmental anomalies of the pelvic organs are aptly illustrated by radiographs following lipiodol injections.

The section on inflammatory diseases of the vulva is beautifully illustrated by a number of colored plates. Weibel regards kraurosis as a later stage of leucoplakia. He regards vaginismus as a purely psychic condition. In a discussion of non-inflammatory diseases of the uterus he considers endometriosis on the heterotopic theory of Robert Meyer. Apparently myomectomy is not an operation of choice in this clinic. The total extirpation of the myomatous uterus is practiced consistently in opposition to supravaginal hysterectomy. Roentgen therapy of uterine myomas has, in Weibel's opinion, a very limited field.

Gradation of carcinoma in relation to treatment apparently gives the same results as obtained in this country. Both preoperative and postoperative roentgen therapy are used in connection with the radical operation. Weibel does not feel that there is much final difference in the results of operative or radiation therapy, if the primary operative mortality for the radical operation be taken into consideration. Weibel lays stress on the Schillër method of diagnosing carcinoma of the cervix and does not feel that the true picture is always revealed by test excision.

A novelty in illustrating changes in position of the uterus consists in the use of a large number of suitable frozen sections of pelves showing various types and forms of prolapse. Sterility and contraception are discussed in consecutive chapters. Weibel believes more information is gained from lipiodol salpingographs than from pertubation of the tubes. He also feels that sterilization should only be practiced under the strongest indications, and after consultation.

There is a full consideration of the technique of radium and roentgen therapy, and other types of physical therapy.

While the section on operative therapy is limited, typical operations are beautifully illustrated. The book serves as an excellent companion volume to the section on obstetrics; together they may be regarded as a well-balanced exposition of the healing art for women.

—Philip F. Williams.

The sheer artistry of both text and illustrations of the second edition of *Control of Conception*[4] by Robert Latou Dickinson, makes its perusal a delight. This is a most important contribution to preventive medicine which, in this edition, has been brought fully up to date. Throughout, the author has sought for security and simplicity. Every phase of the subject is covered; effectiveness, the variations necessary to meet different general and local conditions such as, for example, the bride, extreme ignorance and poverty, as in the coolie, the treatment of patients with prolapse, are all taken up. This is a true source book of sex anatomy, methods of contraception and allied subjects. It fully meets with the crying need for help to the physician, and through him, to the laity.

—R. T. Frank.

A short brochure on the *Vaginal Diaphragm*[5] by Clark, contains full details on its use as well as that of contraceptive jelly, the sole method discussed. Every

[4]**Control of Conception.** By Robert Latou Dickinson, M.D., Former Clinical Professor of Obstetrics and Gynecology, Long Island College Hospital, etc. A clinical medical manual with numerous original illustrations by the author. Second edition, 390 pages. Williams & Wilkins Company, Baltimore, 1938.

[5]**The Vaginal Diaphragm.** By Dr. Le Mon Clark, Chicago. Illustrated, 107 pages. The C. V. Mosby Co., St. Louis, 1939.

detail is entered into for the benefit of the physician. The special aim of the book is to enable the physician to instruct patients correctly.

—*R. T. Frank.*

In Quinet's *Histophysiology of the Menstrual Cycle,*[6] two-thirds of the monograph is devoted to a very careful analysis of the morphologic, physiologic, and biologic literature of the subject. His personal observations deal with uterine biopsy and vaginal smears, particularly in castrates, and the effect upon these of hormone therapy. While the monograph contains nothing new, it is a very excellent and well-gotten up résumé.

—*R. T. Frank.*

Bourne and Williams' *Recent Advances in Obstetrics and Gynaecology*[7] has reached the fourth edition. As previously, very selected subjects have been chosen for exposition. For example, under obstetrics, remarks on ante-partum hemorrhage, pyelitis, puerperal sepsis may be mentioned; under gynecology, cancer of the uterus, sterility, prolapse, sympathectomy, and the sex hormones. The book does not replace the American Year Books, as it is not as comprehensive as these. On the other hand, the subjects are taken up in much greater detail. The illustrations of the Manchester operation might well bear redrawing as they do not illustrate the technical steps adequately. The reviewer must take exception to the statement on page 258 that "In any case, to form an idea of urinary oestrone excretion, in the presence of abnormality, it would be necessary to estimate the excretion every day for a month, which is manifestly impossible in clinical work." Certainly in many hospitals in this country as well as abroad, innumerable cases have been investigated over periods of a month.

—*R. T. Frank.*

Feminine Hygiene in Marriage[8] is a short book written by a layman. It contains "information to aid the married woman to meet the special problems of her sex." It is a "home" book for the laity, containing true information which, however, might be readily misinterpreted. For example, it lauds vaginal tampons instead of napkins, with which advice most physicians would disagree.

—*R. T. Frank.*

Obstetrics

The most characteristic features of this new work, entitled *Clinical Obstetrics,*[9] are due to the fact that its author, Dr. Mudaliar, is Professor of Obstetrics in the University of Madras. His book is distinctly adapted to specific local needs both in teaching and in practice. Problems and methods of treatment of special practical importance are stressed and described in detail. Thus in the extensive discussion of diseases complicating pregnancy we find a special chapter devoted to Tropical Diseases. Since "pernicious anemia of pregnancy is very common in tropical countries" the 12 pages assigned to anemia include a description of the methods of hematologic examinations. The high incidence of malaria among pregnant women in India easily explains why in the description of differential diagnosis of eclampsia the item of Cerebral Malaria has been included. It is only natural that the volume

[6]**Histo-Physiologia do Cyclo Menstrual.** Par Dr. Antonio A. Quinet. Officinas Graficas de A. Noite, Rio de Janeiro, 1938.

[7]**Recent Advances in Obstetrics and Gynaecology.** By Aleck W. Bourne, Obstetric Surgeon to St. Mary's Hospital, etc. and Leslie H. Williams, Senior Obstetric Surgeon to Out-Patients, St. Mary's Hospital, etc. University of Cambridge. Fourth edition, with 98 illustrations, 366 pages. Blakiston's Son and Co., Philadelphia, 1939.

[8]**Feminine Hygiene in Marriage.** By A. F. Niemoeller, A.B., M.A., B.S. Illustrated, 155 pages. Harvest House, New York, 1938.

[9]**Clinical Obstetrics.** By A. Lakshmanaswami Mudaliar, Professor of Obstetrics, University of Madras, Medical School, etc. With 204 text illustrations and 9 in color, 819 pages. Oliver and Boyd, Edinburgh, Tweedale Court, 1938.

offers much information concerning osteomalacia, "which is fairly common in North India but practically unknown in South India."

In a textbook of obstetrics, which takes cognizance of such modern information as Caldwell-Moloy's classification of pelves, warns against Schultze's swinging, mentions the usefulness of Willett's forceps in treatment of placenta previa and describes the value of sulfanilamide, one is somewhat surprised to find in connection with the therapy for exaggerated vomiting of pregnancy, recommendations such as oral administration of cerium oxalate, cocaine, Lugol's solution, dilute hydrocyanic acid and cocainization of the eroded cervix.

The author expresses precisely his own views and advocates the methods which have proved most useful in his own hands. In this connection his interesting observation may be mentioned that in cases of hydatid mole, the chances of an invasion of cells and thus for a chorioepithelioma are greater if the vesicles of the mole are very small.

As far as style of language, arrangement of material and typography are concerned, the volume deserves unstinted praise.

—*Hugo Ehrenfest.*

The close relation of *Midwifery*[10] by Ten Teachers to *The Abnormal in Obstetrics*[11] by Sir Comyns Berkeley, Victor Bonney and Douglas MacLeod makes it convenient, if not essential, to discuss both these volumes conjointly.

After but three years it became necessary to prepare a new sixth edition of the widely appreciated *Midwifery* by a slightly altered group of obstetricians, all teachers in London. In regard to this well-known book it will suffice to state that many eliminations and additions have been made both in the text and in the illustrations, undeniably enhancing the value of this compact textbook. It seems, however, noteworthy that for the first time illustrations of the low cervical cesarean section have been included. Willett's forceps, attached to the fetal scalp for the purpose of traction which, we believe, is but rarely used in this country, is mentioned and recommended, e.g., in connection with the treatment of hemorrhage from placenta previa or again for lifting the fetal head out of the pelvic inlet in the low cesarean section.

As well characterized by the volume just reviewed British textbooks of obstetrics as compared with the respective American standard textbooks in general limit themselves to the presentation of essential facts. For this reason it becomes necessary also to write books useful "to those ambitious of passing one of the higher examinations in obstetrics" or "to those in whose work midwifery plays an important part." We feel that *The Abnormal in Obstetrics* in this country will appeal particularly to the latter group. The deliberate omission of details in regard to anatomy, physiology, and operative procedures as useless repetition readily explains the almost complete absence of illustrations. The topics authoritatively discussed among others are Sterility, Endocrine Anomalies, Toxic States, Complicating Diseases of the Mother, Anomalies of the Genital Tract, Complications During Delivery, Puerperal Sepsis, Diseases of the Breast, Diseases, Injuries and Malformations of the New-Born. The two concluding chapters are devoted to Blood Transfusion (illustrated) and Analgesia, respectively.

The volume begins with a somewhat startling sentence: "Pregnancy is a state induced by a neoplasm." In some aspects the rapidly growing fetus might be compared with a neoplasm, but we regret that in pointing out the many similarities between these two conditions the authors fail to emphasize the obvious fact that unlike any other neoplasm the fetus exerts a definitely beneficial, stimulating effect on the function of almost all maternal organs. Thus pregnancy is probably not

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[10]**Midwifery.** By Ten Teachers, under the direction of Clifford White, Obstetric Surgeon, University College Hospital, etc. Edited by Sir Comyns Berkeley, Clifford White and Frank Cook. Sixth edition, 262 illustrations and 9 color plates, 676 pages. William Wood & Company, Baltimore. 1938.

[11]**The Abnormal in Obstetrics.** By Sir Comyns Berkeley, Consulting Obstetric and Gynaecological Surgeon of the Middlesex Hospital, London, etc., Victor Bonney, Consulting Obstetric and Gynaecological Surgeon to the Middlesex Hospital, etc., and Douglas MacLeod, Assistant Obstetric Surgeon, St. Mary's Hospital, etc. First edition, six illustrations, 525 pages. William Wood & Company, Baltimore, 1938.

correctly qualified as standing alone among all physiologic processes in that, while the others serve the good of the individual, "reproduction is exercised for the benefit of the race at the cost of the individual." The cost, admittedly, is still too high and might well be expected to become lessened if every practitioner would become thoroughly familiar with all the important facts presented in this volume.

—*Hugo Ehrenfest.*

Beginning this review with a summary, which customarily concludes it, we state that this *Text-Book of Obstetrics*[12] of the Queen Charlotte's Maternity Hospital in London, now appearing in its fifth edition, admirably fulfills its purpose of setting forth precisely the views held and methods practiced by its clinical staff. Confusing descriptions of theories or varieties of opinion and treatment are avoided.

Obviously one looks for striking and noteworthy differences in British and American practice. In all the more important questions they are hardly noticeable, though careful reading of the book leaves one with the definite final impression that British obstetric methods are more conservative. Patients still are examined and delivered in the side position. Episiotomy, described not in connection with delivery of the head but in the section entitled Abnormal Labor, is referred to as "sometimes advisable." The treatment of even severely toxemic patients is strictly limited to dietetic management (detailed diet lists are given) and other therapeutic procedures, as commonly applied in our country, seem to be instituted only after convulsions have set in. Great stress is put on Stroganoff's conservatism in dealing with eclampsia. Chiefly for the purpose of avoiding unnecessary cesarean sections a clear and extensive discussion of trial labor is offered. A relatively large amount of space (over 50 pages) is devoted to an exhaustive consideration of puerperal sepsis. Sulfanilamide preparations "show great promise of completely altering the outlook, at any rate in infections with the hemolytic streptococcus."

No percentage figures are given for the incidence of forceps extractions, cesarean sections or other operations in the Queen Charlotte's Maternity Hospital but, judging from the entire tone of the volume and the quoted reference to episiotomy, there can be no doubt that our operative interference is decidedly higher. Thus naturally the question suggests itself: Does the evident conservative trend of British obstetrics yield better results?

Maternal mortality figures, as is well known, are not directly comparable but, in regard to maternal loss, disappointment is expressed in the fact that it has not been noticeably decreased within the last forty years and still stands for England and Wales at about 4 per 1,000 births (Denmark 2.6; Norway 2.8). In contrast the infant death rate during the same period of time has declined from 156 to the present rate of 59 per 1,000 births.

This in itself would seem most satisfactory were it not for the subsequent statement that in a recent series of breech labors in this hospital "the *gross* fetal and neonatal mortality reached the alarming figure of 37 per cent." So it seems that good obstetrics lies somewhere between British conservatism and American radicalism.

—*Hugo Ehrenfest.*

In the course of a few years it became desirable to revise extensively this new fifth edition of *Stoeckel's Textbook of Obstetrics.*[13] Considerable obsolete matter was eliminated, a good deal of new material added and numerous alterations made in the illustrations. The death of Professor von Franqué necessitated some changes in the staff of the nine collaborators which includes most of the heads of large German womens' clinics.

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[12]**The Queen Charlotte's Text-Book of Obstetrics.** By Members of the Clinical Staff of the Hospital. Fifth edition, with 4 colored plates and 293 text figures, 668 pages. J. & A. Churchill Ltd., London, 1938.

[13]**Lehrbuch der Geburtshilfe.** Herausgegeben von Professor Dr. W. Stoeckel, Universitaets Frauenklinik in Berlin. Fifth revised edition, with 639 illustrations, the most of which are colored, 1054 pages. Verlag von Gustav Fischer, Jena, 1938.

It is obvious that in the hands of such experts the numerous problems constituting the science and practice of obstetrics are presented both exhaustively and authoritatively. As is practically inevitable in a work of collaboration of this sort, there can be noticed a certain disproportion in space given to the consideration of some topics. The American reader cannot fail to observe that in German obstetric practice relatively little importance is assigned to blood transfusions or roentgenography, especially in its applicability to pelvimetry. Possibly for this reason no reference is made to the work of Caldwell or Thoms. An outstanding feature of this volume is the abundance of excellent illustrations, particularly of those reproducing natural color photographs.

—*Hugo Ehrenfest.*

Devraigne has given a glance at obstetrics throughout the ages.[14] In it he has attempted to condense the three big volumes written by de Siebold and Hergolt which cover the entire history of obstetrics. The illustrations are mainly from Witkowski. He starts with the midwife in the Bible, pre-Hippocratic and Hippocratic medicine, mentions that Celsus described version and embryotomy. Soranus was the first one to use podalic version to extract the live fetus. The entire history of obstetrics is divided into eleven epochs. The text is short, profusely illustrated, and forms a handy epitome.

—*R. T. Frank.*

The second edition of Burckhard's *Obstetric and Gynecological Therapy* with inclusion of drug treatment[15] is designed for rapid orientation of the problems which confront the practitioner. The material is arranged alphabetically. Big interventions are just indicated, while those which fall into the working sphere of the general practitioner are described in detail. Many of the methods are no longer acceptable here, as for example, dilatation with laminaria in inevitable abortion, or irrigation of the cavity of the uterus with antiseptic solutions after emptying. Thirty-three closely printed pages cover the numerous drugs suggested, the vast majority of which are trade preparations quite unknown in this country.

—*R. T. Frank.*

The series on Urology edited by Boeminghaus, cover two special aspects.

Ottow describes the *Urological Indications for Interruption of Pregnancy.*[16] The monograph of 27 pages describes various urologic complications of pregnancy, whether they require or do not require interruption. Throughout, the conservative viewpoint is emphasized.

—*R. T. Frank.*

Rubritius, in the compass of 22 pages, takes up the *Spasm of the Vesical Sphincter.*[17] The hypertonic sphincter may cause the same symptoms and bi-effects as prostatic hypertrophy. The cause may be local or from the spinal cord. For the cure he advises his own operation, requiring a wedge-shaped open excision of the sphincter ring in preference to transurethral section.

—*R. T. Frank.*

De Moraes has written a book for expectant mothers of which this, *Sa Maternidade,*[18] is the second edition. It is simple and contains both prenatal and postnatal advice.

—*R. T. Frank.*

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[14]**L'Obstétrique a Travers les Ages.** Par L. Devraigne, Accoucheur de Lariboisiére, etc. With 77 illustrations, 138 pages. Gaston Doin & Cie., Paris, 1939.

[15]**Geburtshilfliche und Gynaekologische Therapie,** mit Einschluss der Heilmittel. Von Dr. Georg Burckhard, o. Professor der Geburtshilfe und Gynaekologie, Universitaet Wuerzburg. Second revised edition, 260 Seiten. Verlag von Ferdinand Enke, Stuttgart, 1938.

[16]**Schwangerschaftsunterbrechung aus Urologischer Indikation.** Von Professor Dr. B. Ottow in Berlin. 27 pages. Verlag von Georg Thieme, Leipzig, 1939.

[17]**Die Hypertonie des Inneren Blasensphinkters.** Von Professor Dr. Hans Rubritius in Wien. 22 pages. Verlag von Georg Thieme, Leipzig, 1938.

[18]**Sa Maternidade.** Par Prof. Arnaldo de Moraes. Second edition. Graphica Sauer, Rio de Janeiro, 1938.

Several years ago the late Professor Sedgwick complained that unfortunately the obstetrician is inclined to look upon the newborn infant as an inevitable by-product of his successful effort to separate the fetus from the mother. Conditions have changed since then. In most obstetric departments and maternity hospitals the newborn ward now is more or less under the control of the pediatric staff. Textbooks of obstetrics devote an ever increasing amount of space to the consideration of the physiology and pathology of the newborn.

For some time a short elective course has been offered to the seniors in the Johns Hopkins Medical School. The material covered in these special lectures, in amplified form, has been presented by Emerson L. Stone in a little volume, entitled *The New-Born Infant. A Manual of Obstetrical Pediatrics,*[19] now published in a second, revised edition. However, this subtitle does not fully reveal the sum total of useful information it contains.

The author discusses thoroughly, from the viewpoints of prevention, diagnosis, and treatment, not only care and feeding of the well or sick infant but also deals competently with specific problems of interest among others to the dermatologist, neurologist, internist, or orthopedic surgeon.

—*Hugo Ehrenfest.*

Endocrinology

In 1936 Van Dyke published *The Physiology and Pharmacology of the Pituitary Body.* He now adds Volume II[20] which is a critical digest of the experimental and clinical literature on the pituitary body that has appeared from 1935 to 1937, with some reports of 1938. The bibliography covers 1,418 titles.

The main subjects dealt with are the anatomy of the pituitary; regulation of growth by the pituitary body; gonadotropic hormones including those in pregnancy and neoplasms; the lactogenic hormone and thyrotropic hormone; the various relationships between the anterior pituitary and the adrenals; the effects on metabolism, and the effect on chromatophores and pigmentation.

The author has changed his opinion and now believes that the posterior lobe is an important gland of internal secretion, with particular effect on water metabolism. This digest is a valuable contribution.

—*R. T. Frank.*

The second edition of *Sex and Internal Secretions*[21] under the editorship of Edgar Allen is, as before, a cooperative survey of advances in researches of internal secretion in relation to sex. As in the previous edition, the Committee for Research in problems of sex of the National Research Council, has aided with its support. This 1,346 page volume is encyclopedic in scope and will prove a valuable source book for those interested in laboratory research. The book is divided into five sections, covering the biologic basis of sex; the physiology of the sex glands, germ cells and accessory organs; biochemistry and assay of gonadal hormones; the hypophysis and the gonadotropic hormones of blood and urine in relation to the reproductive system; and additional factors in sex functions and endocrine applications in man. Twenty-seven contributors have covered this immense field.

In spite of the many contributors, the text, on the whole, is even, and few repetitions or contradictions are noted. The main interest has been focused to give a broad and yet detailed outline of the bewildering number of individual researches found in the literature, and by means of this, to give as complete a picture as the present state of our knowledge will permit. In this, the authors have been, on the

[19] **The New-Born Infant.** A Manual of Obstetrical Pediatrics. By Emerson L. Stone, M.D., Associate Clinical Professor of Obstetrics and Gynecology, School of Medicine, Yale University, etc. Second edition, thoroughly revised, 291 pages. Lea & Febiger, Philadelphia, 1938.

[20] **Physiology and Pharmacology of the Pituitary Body.** Volume II. By H. B. Van Dyke, Head of Division of Pharmacology, Squibb's Institute for Medical Research, etc. Illustrated, 402 pages. University of Chicago Press, Chicago, 1939.

[21] **Sex and Internal Secretions** A Survey of Recent Research. Editors: Edgar Allen, Yale University; Charles H. Danforth, Stanford University; and Edward A. Doisy, St. Louis University, with foreword by Robert M. Yerkes, Yale University. Second edition, illustrated, 1346 pages. Williams and Wilkins Company, Baltimore, 1939.

whole, successful. It is impossible in the scope of a review, particularly of a second edition, to give even a slight résumé of the content. In speaking of the origin of the gonads, it is said "the gonad-forming area contains the fundamental material for the formation of the sex cells." Yet removal of the germ cell crescent of Swift, which is an extraembryonic area, produces absence of the germ cells. Chorionic fusion of heterosexual twins causes the masculinized freemartin in cattle and possibly in the pig, but not in the cat, peludo, marmoset or man, showing that such fusion varies in effect in different species. The evolutionary history of the endocrines is just beginning to attract attention but is already of great interest.

Although a very conservative point of view is noted throughout the text, statements which appear distinctly hazardous, occasionally are noted. For example, that attempts to cure sterility by hormone therapy are readily frustrated by the antihormone action set up in the patient. In the opinion of the reviewer, many other factors might account for ill success. The surmise that the normal rate of the human ovarian production of estrogens is 500,000 International Units per day is not borne out by the many blood bio-assays so far described in the nonpregnant. No more than 25 to 35 units of estrogenic activity have ever been demonstrated. A very conservative standpoint is well demonstrated by the fact that the placenta is only considered as a *possible* endocrine gland (the italics are mine). . . . "The evidence is strong but falls short of rigid proof."

While the major portion of the book will be of interest chiefly to the laboratory investigator, the concluding section contains such clinically important subjects as the relation of vitamins to the sex glands; the sex drive and sex function in man. This last chapter can be read with profit particularly by the over-optimistic endocrinologists who will find that although the results of therapy are of extreme importance, up-to-date, negative results far overshadow positive achievements.

—*R. T. Frank.*

August Mayer has written a short monograph on the *Constitution in Obstetrics and Gynecology.*[22] This interesting sketch takes up normal and abnormal constitution, particularly the physical and psychologic sex differences. Body types versus disposition to diseases are described. Considerable importance is attached to the development of the teeth and palate. A detailed description of the effects of infantilism, particularly on the genital tract, is given. Included are other characters of this group such as the physical and mental, the frequency of dysmenorrhea, susceptibility to myoma and cancer. Many of the illustrations are borrowed from Stratz, Sellheim, and other classic sources.

—*R. T. Frank.*

Miscellaneous

Problems of Ageing[23] is a symposium under the editorship of E. V. Cowdry, sponsored by the Josiah Macy, Jr., Foundation, and likewise indirectly by the Union of American Biological Societies and the National Research Council. There are twenty-six contributors, well known in their line. The book is 758 pages in length and covers the subject as adequately as the present state of our knowledge permits.

The contents is extremely fascinating, beginning as it does with the aging of plants, covering the senescence and death in protozoa and invertebrates, the ageing of insects, and of vertebrates. It then takes up human cultural levels, including anthropometry of old age, length of life, age differences in illiterate societies, attitude toward the aged, and similar subjects. Longevity, in the past and future, based on statistical tables is discussed.

Next the effect of age on the various organ systems is dealt with. Best known appeared to be the cardiovascular, digestive, skeletal and locomotor, as well as the

[22]**Die Konstitution in der Geburtshilfe und Gynaekologie.** Von Professor Dr. August Mayer, Direktor der Universitaets-Frauenklinik in Tuebingen. With 42 illustrations, 57 pages. Verlag von Ferdinand Enke, Stuttgart, 1938.

[23]**Problems of Ageing.** Biological and Medical Aspects. Edited by E. V. Cowdry, Washington University in St. Louis. 121 illustrations, 758 pages. Williams & Wilkins Company, Baltimore, 1939.

effect of age on the skin. The effect of age on the endocrine glands, including the sex glands, the effect of age on personality and psychosexual phenomena, aging of the nervous system and the special senses, are all included.

The psychologic aspects of aging, the changes in the chemical, and homeostatic mechanisms, the body fluids, and tissue susceptibility, are discussed. Finally, aging from the viewpoint of the clinician concludes this very careful study.

One gathers that as the proportion of older individuals in the population increases, the medical and social importance of age becomes more and more important. The biologic consideration of growth, development, maturation and senescence in all living organisms has been considered from two viewpoints, the one, the inevitable involution, the other, the effect of outside influences, such as infection, trauma, etc., that is, the effect of various environments upon aging. Differently put, it includes normal senescence versus the pathology of old age. The object is not only the conservation of life, but the increase of well being in older individuals.

The world at present is confronted with a declining total population and an increase in the older members of its constituents. In this mechanical age, there is a premium on youthful vigor with a great discount on experience which shows itself in a restriction of child labor and the strong movement for old age pensions. As experience is considered of such little value, particularly in industry, it is important to try to develop activities in which the aging group can engage with most satisfaction to themselves and most benefit to the community. John Dewey says that the many perplexing problems which now attend human old age have an important psychologic-social origin.

—*R. T. Frank.*

Dr. Behan began this volume on *Cancer*[24] as a treatise on cancer of the breast. In order to elucidate the problems of that condition he found it necessary to incorporate a comprehensive discussion of the biologic history of malignancy with the result that his effort gives us a splendid consideration of the subject of malignancy. The book should be of tremendous value to anyone who is not intimately concerned in the work of the general cancer clinic, and even to such workers the detailed documentation will make the book an exceedingly valuable reference volume and source of bibliography.

There are thirty-nine chapters in the text. It begins with a general consideration of cancer which he classes as a "biological variation in which the cells have acquired a high power of development of multiplication but have lost the power of contact." The statistical analyses show the importance of the cancer problem. It is stated that in twenty years the incidence of cancer of the breast in women of the United States increased 50 per cent. Such relationships as nutrition, race, sex, age, and the like are brought out. The etiologic factors are discussed from the standpoint of systemic organs, heredity, familial disposition, immunity against cancer, and the dysfunctions of the endocrine glands. The relationship between ovarian dysfunction and cancer of the breast is considered at length, and should be of interest to gynecologists and obstetricians. Behan states that there is a considerable doubt whether chronic irritation alone is sufficient in the absence of any inherent cell defect or inherited tendency to cause a malignant growth. He feels that both the benign and malignant processes are probably produced by the same initial underlying causative statement.

Pathology and pathologic physiology of cancer of the breast are fully taken up. Clinical aspects of symptoms and subjective signs are presented in a thorough fashion. The author devotes a long chapter to noncancerous tumors of the breast, then proceeds to diagnosis and diagnostic tests, following which he considers metastases developing in the course of the mammary carcinoma. He discusses the statistics regarding prognosis, which throw light on the various factors which may influence life expectancy in this condition. Behan discusses the various methods of operative and nonoperative treatment and a detailed presentation on pre- and

[24]**Cancer,** with special reference to Cancer of the Breast. By R. J. Behan, M.D., F.A.C.S., Cofounder and Formerly Director of the Cancer Department of the Pittsburgh Skin and Cancer Foundation. Illustrated, 844 pages. The C. V. Mosby Company, St. Louis, 1938.

postoperative radiation. The various operative methods and anatomic relations underlying them are fully illustrated together with the indication and selection for the various types of operation.

In the next part of the book, he proceeds to the subject of constitutional treatments which here, probably for the first time, has been given special consideration. He discusses the psychology of the cancer case, hygiene and diet, the literature on the composition of diets which will influence the regression of cancer. He further, under constitutional treatment, discusses the value of chemotherapy, with the proposed effects that certain biologic products and chemicals may exert upon cancer cells. He states in regard to lead, which at one time was proposed in the treatment of cancer of the breast and uterus, that its usefulness has been greatly overestimated, and the enthusiasm for its use had reached far beyond its possibility for cure. He devotes sixteen pages to the present aspects of organotherapy, but concludes that experimental evidence seems to indicate that "endocrines" are not of any value in treatment. The subject of irradiation by both x-ray and radium is voluminously considered from every possible angle; dosage, technique, results, use in metastases, use in multiple tumors, and so forth. Behan calls attention to the fact that the cancer of the breast patient from time to time should be released from treatment in order to build up his psychology and mental reserve.

While the context of the book is based upon the problem of cancer of the breast, the comprehensiveness of the general problems, the wise evaluation of theories and methods of treatment, and the extensive documentation should make this a book of unusual value.

—*Philip F. Williams.*

Handbook on Cancer[25] was prepared by the Committee on Cancer Control of the Canadian Medical Association for the general practitioner. It is elementary but informative, dealing with the recognition and treatment of cancer in all the organ systems. It is sufficiently detailed to be of real use as a primary source book for the practitioner.

—*R. T. Frank.*

The second edition of Cole and Elman, *Textbook of General Surgery*,[26] as previously, is designed for practitioners and medical students. It is largely based on the third year course for medical students at Washington University. The book has evidently filled a real demand because the second edition follows three years after the first. Because of this, no change in the paging has been attempted but by means of judicious deletion and printing in small type, such new subjects as sulfanilamide, vitamin K in bleeding of jaundice, decompression of the intestinal tract in obstruction, the histamine glare test to determine level of amputations, and the more conservative attitude toward pancreatic necrosis have been included. The book is over a thousand pages in length, and contains 559 illustrations. It is well written, comprehensive and up to date. Each chapter has its short bibliography and there is even an authors' index. The book seems to fulfill its purpose most adequately.

—*R. T. Frank.*

As indicated in its title, *The Fundamentals of Internal Medicine*,[27] this volume, written by many collaborators and edited by Wallace Mason Yater, is designed primarily for the student. As stated in the Preface this work is intended to provide

[25] **Handbook on Cancer,** for the medical profession. The Authorship Committee, Department of Cancer Control, Canadian Medical Association, Toronto, 1938.

[26] **Textbook of General Surgery.** By Warren H. Cole, Professor of Surgery, University of Illinois, College of Medicine, etc., and Robert Elman, Associate Professor of Surgery, Washington University School of Medicine, St. Louis. Second edition, 559 illustrations, 1031 pages. D. Appleton-Century Company, New York, 1939.

[27] **The Fundamentals of Internal Medicine.** By Wallace Mason Yater, Professor of Medicine and Director of the Department of Medicine, Georgetown University School of Medicine, etc. First edition, with 255 illustrations, 1021 pages. D. Appleton-Century Company, Inc., New York, 1938.

the foundation upon which the superstructure of more detailed and extensive knowledge may be built. In concise and systematic arrangement that "minimum amount" of information is presented, which "a student or general practitioner should have at his fingertips." Outstanding features of this book are the well-selected illustrations, many instructive tables, mostly referring to essential points in differential diagnosis, and its final section (XXI) dealing with diet in general and specific diets in various diseases.

—Hugo Ehrenfest.

The second edition of Meakins, *The Practice of Medicine*,[28] is a volume of more than 1,400 pages which has brought this book fully up to date. It is a pleasure to encounter a vividly written, a well and profusely illustrated textbook of medicine. The illustrations add greatly to the value of the text, are 521 in number, including many colored plates, and cover x-rays, electrocardiograms, charts, and graphs, in addition to the depiction of such lesions which lend themselves to photography as well as many sections and microphotographs of organs. Symptomatology is stressed but laboratory aids are not undervalued. The book is designed for the student and practitioner. It covers every phase of internal medicine. Certain chapters have been written by other authors: the nervous system by Petersen, the urinary by Scriver, the metabolic disorders and glands of internal secretion by Mason.

This is a very excellent textbook which covers the field most adequately and is designed for quick reference as well as continuous reading.

—R. T. Frank.

The customary strict division between the profession of medicine and dentistry admittedly has delayed adequate appreciation of the rôle played by dental pathology in the causation of various diseases. The medical student, in the interest of public health, must become familiar at least with the basic facts of modern dental science. From this viewpoint McCall's small volume, dealing with the *Fundamentals of Dentistry in Medicine and Public Health*,[29] can be said to fill a long felt want.

The obstetrician necessarily is interested in the intimate dental and systemic interrelations in two respects: The possible effect of infected mouth or teeth on the health of the pregnant woman and the preservation of teeth already deciduous during pregnancy. The significance of dental focal infection in the origin of certain types of toxemia is generally appreciated.

In the author's belief proper attention consists in a combination of expert dental care with a dietetic regime that will guarantee adequate food intake containing both quantitative needs and the proper proportion of essentials. The mineral metabolism in this respect is of greatest importance.

It seems noteworthy that the author, a dental specialist, does not mention oral administration of calcium. Many obstetricians routinely advise this medication which actually is indicated and justified only under certain conditions. A Report of the Council of Pharmaceutics of the American Dental Association (1936) contains the definite statement: "The evidence in favor of administration of calcium compounds (during pregnancy) is not of such nature as to warrant the claims that supplies of calcium or of phosphorus supplemental to that obtained by diet are necessary." Recent obstetric literature strongly suggests that an excess of calcium intake might induce abnormal ossification of skull bones or lead to noxious calcification of the placenta.

Careful perusal of this book must be recommended to all practitioners, especially to those interested in obstetrics.

—Hugo Ehrenfest.

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[28]**The Practice of Medicine.** By Jonathan Campbell Meakins, M.D., Professor of Medicine and Director of the Department of Medicine, McGill University, etc. Second edition, with 521 illustrations including 43 in color. The C. V. Mosby Company, St. Louis, 1938.

[29]**Fundamentals of Dentistry in Medicine and Public Health.** By John Oppie McCall, Director of the Murry & Leonie Guggenheim Dental Clinic, New York, etc. 50 illustrations, 161 pages. The Macmillan Co., New York, 1938.

Landmarks in Medicine[30] are seven lectures delivered to the laity under the auspices of the New York Academy of Medicine. The subjects dealt with are the history of medicine, the development of research, the progress in x-ray, the subject of longevity, and the activities of the medical examiner featuring the improvement following the abolishment of the antiquated coroner's system. These lectures are readily understood and informative, having been delivered by well-known specialists in each field.

—*R. T. Frank.*

Clinical Laboratory Methods and Diagnosis[31] after only three years appears in a second edition. This volume of over 1,600 pages covers every phase of laboratory diagnosis. In the new edition all of the recent advances have been incorporated. This applies particularly to the newer conceptions on nephritis and nephrosis, the expansion of the chapter on hematology, as well as that on parasitology and tropical medicine.

All the various laboratory methods of diagnosis are dealt with, including bacteriology, serology, post-mortem examination and toxicology. This is a very complete exposition of the subject which should be of great use to all engaged in laboratory work. The subject matter is so large that it does not lend itself to detailed review.

—*R. T. Frank.*

The Genuine Works of Hippocrates[32] translated from the Greek by Francis Adams LL.D., Surgeon, is a reprint reproducing the first English translation of 1849 of Francis Adams, a Scottish surgeon. In this edition, no footnotes are appended. Those interested in medical history will find it pleasant reading.

—*R. T. Frank.*

Alcohol in Moderation and Excess by Waddell and Haag[33] was primarily written for the school system of the state of Virginia. It was designed to be used as a source book for teachers in instruction in physiology and hygiene, on account of the law of Virginia which made it mandatory to give, in the courses in physiology and hygiene, a view of the evil effects of alcohol and other narcotics on the human system. The book, in spite of its excellence and objectivity, was rejected by the legislature. It contains much of interest, including the effect of alcohol on auto accidents, insanity; the food value of alcohol; its effect on basal metabolism and other physiologic bi-effects.

—*R. T. Frank.*

Consultation Room[34] by Frederic Loomis of Oakland, California, is a selection of episodes and anecdotes from twenty years of the author's medical life in which he has "selected problems of human lives and human relations, counterparts of which are factors in the interesting but perplexing life of every physician."

These autobiographic sketches of a gynecologist and obstetrician contain crisp and attractive episodes beginning with his early life, his start in medical school, through his internship, and later activities in practice. Apparently selected at random, it will be found that each has its reason and that the whole illuminates many phases which rarely are enlighteningly touched upon and described for the laity. The style is interesting, the anecdotes amusing, some of the episodes touching and showing the trials and temptations to which a physician is subjected, as well as the difficulties encountered in treating his patients intelligently and fairly.

—*R. T. Frank.*

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[30]**Landmarks in Medicine.** Laity Lectures of the New York Academy of Medicine. Introduction by James Alexander Miller, M.D., President of the Academy. D. Appleton-Century Company, New York, 1939.

[31]**Clinical Laboratory Methods and Diagnosis.** A Textbook of Laboratory Procedures with Their Interpretation. By R. B. H. Gradwohl, M.D., Director of the Gradwohl Laboratories, etc. Second edition, with 492 illustrations in the text and 44 color plates, 1607 pages. The C. V. Mosby Company, St. Louis, 1938.

[32]**The Genuine Works of Hippocrates.** Translated from the Greek by Francis Adams, LL.D., Surgeon. The Williams & Wilkins Company, Baltimore, 1939.

[33]**Alcohol in Moderation and Excess.** By J. A. Waddell, M.D., Professor of Pharmacology, Materia Medica and Toxicology, Medical Department, University of Virginia, and H. B. Haag, M.D., Professor of Pharmacology, Medical College of Virginia. William Byrd Press, Inc., Richmond, Va., 1938.

[34]**Consultation Room.** By Frederic Loomis, M.D. Alfred A. Knopf Inc., New York, 1939.

Society Transactions

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF MARCH 2, 1939

The program was as follows:

Herniation of Amniotic Sac Into the Subcutaneous Tissues in a Pregnancy Following Cesarean Section. Dr. Franklin M. Kern.

Nephrectomy During Pregnancy. Dr. George L. Hoffman. (For original article, see page 514.)

Studies on the Concentrations of Estrogenic and Gonadotropic Hormones in the Serum of Pregnant Women. Dr. A. E. Rakoff (by invitation). (For original article, see page 371.)

Some Summaries in the Technique of Hysterectomy. Dr. E. G. Maier.

X-ray Localization of the Placenta by Soft Tissue Technique and Without the Use of Opaque Media. Dr. R. M. Smith.

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF MARCH 17, 1939

The following papers and discussions were presented:

Surgical Treatment of Bilateral Polycystic Ovaries—Amenorrhea and Sterility. Drs. Irving F. Stein and Melvin R. Cohen. (For original article, see page 465.)

Treatment of the Menopause With Estradiol Dipropionate. Drs. Edward M. Dorr and R. R. Greene. (For original article, see page 458.)

The Complications Associated With Excessive Development of the Human Fetus. Drs. Arthur K. Koff and E. L. Potter (by invitation). (For original article, see page 412.)

(Note: The Transactions of the February meeting will appear in a subsequent issue.)

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Pregnancy and Disease

Reid and Mackintosh: Incidence of Anemia in Pregnancy: Influence of Social Circumstances and Other Factors, Lancet **1**: 43, 1937.

The hemoglobin level was estimated in 1,108 pregnant women; 10.2 per cent gave a reading below 70 per cent. The anemia was always hypochromic. When the women were divided into two groups according to the family income, it was found that the incidence of anemia was higher in the lower income group. Multiparity in women in good social circumstances did not appear to have much influence, except in women with five or more pregnancies. Age, work outside the home, or abnormality in pregnancy had no recognizable influence on the degree of anemia.

J. P. GREENHILL.

Naish, F. C.: A Study of the Immediate and Remote Effects of Pregnancy on Diseases of the Heart, J. Obst. & Gynaec. Brit. Emp. **44**: 659, 1937.

A study of 63 patients during 83 pregnancies over a period of eleven years suggests that pregnancy and its accompanying problems impose a burden upon the damaged heart which leads to permanent crippling. On the other hand, it is likely that the damaged heart would deteriorate during eleven years even in the absence of childbearing, but it has been found impossible to obtain nulliparous control cases. The damage is increased when the pregnancies become multiple. Too frequent pregnancies put more strain on the heart than those more widely spaced.

Syncope is a symptom which indicates a guarded prognosis in cases of aortic reflux. Patients suffering from aortic stenosis do not tolerate pregnancy well. Auricular fibrillation is rare and does not occur at an early age; nevertheless it occurs at an earlier age in parous than in nulliparous women. The prognosis is poor in all cases.

Complete heart block may not be a contraindication to pregnancy. Cases of bundle branch block have a poor prognosis. Hemoptysis is always a sign of congestive failure. Extrasystoles indicate an increased irritability of the affected part, but are common in normal pregnancy. In cases of mitral stenosis auricular extrasystoles may be precursors of auricular fibrillation.

A follow-up of 22 per cent of the patients showed 37 per cent worse than before their pregnancies. The patients in whom the heart was decompensated during pregnancy showed the greatest degree of permanent crippling afterwards. In the opinion of the author antenatal rest for therapeutic and routine purposes is of great value. The question of anesthesia requires consideration of the type of heart disease, the procedure for which the anesthetic is required, and the experience of the anesthetist.

J. P. GREENHILL.

Schultz, W.: Prognosis and Treatment of Circulatory Disease in Pregnancy, Arch. f. Gynäk. **166:** 62, 1938.

The author divides all cardiac disease into three groups determined by compensation, latent decompensation and decompensation. His experiences lead him to conclude that there is no indication to interrupt pregnancy with full compensation. Latent decompensation is an indication for interruption. Decompensation is also an indication but the interruption must never be done during the state of decompensation and must await the re-establishment of complete cardiac compensation. The author feels that pregnancy is interrupted much too frequently, and that pregnancy, labor, and the puerperium are usually less of a strain on the cardiac patient than is the added work of caring for the newborn baby. This feature of proper care of the cardiac patient is all too frequently neglected.

RALPH A. REIS.

Danforth, W. C.: The Management of Pregnancy and Labor in the Presence of Heart Disease, Illinois M. J. **74:** 88, 1938.

Danforth states that the woman with a murmur, whose heart is perfectly compensated, will probably go through pregnancy and labor without trouble. If perfect compensation is present no treatment is needed except to caution the patient against undue exertion, for normal pregnancy alone causes a 50 per cent increase in the work done by the heart. Decompensation in the first trimester of pregnancy demands termination of the pregnancy. Danforth does not believe in premature induction of labor in cardiac cases as this type of labor is frequently unsatisfactory. Morphine and ether are the analgesics of choice. Labor should proceed normally until dilatation becomes complete. Forceps delivery should replace all of the second stage which is not accomplished by the unaided force of the uterine contractions, for no voluntary effort should be allowed. Cesarean section should be used only rarely.

EUGENE S. AUER.

Matthews, H. B.: Pregnancy and Tuberculosis, Am. J. Surg. **35:** 293, 1937.

What is to be done to insure adequate care, both medical and obstetric, for the pregnant tuberculous woman? Matthews offers the following suggestions:

1. The ideal set-up for a tuberculosis and pregnancy clinic would be a special institution devoted exclusively to care and treatment of pregnant tuberculous women. Here would be working in close harmonious cooperation a specialist in tuberculosis, an expert obstetrician interested in tuberculosis, a pediatrician interested in tuberculosis, a roentgenologist and the whole group supported by good pathologic and bacteriologic laboratories.

2. In lieu of this ideal set-up, it is proposed that the hospital allocate a certain number of beds for pregnant tuberculous women and that these patients be under the direct supervision of a tuberculosis specialist in cooperation with an obstetric specialist. After the seventh month of pregnancy the obstetrician should assume first control of the patient, with the tuberculosis specialist cooperating. The obstetrician is to continue in charge until after the postpartum period (two or three weeks or longer), following which the tuberculosis specialist again assumes charge and manages the case as he would any other case of tuberculosis.

Management of the baby should be put under direct supervision of a pediatrician interested in tuberculosis as soon as the umbilical cord is ligated. The baby should never be allowed to nurse, except perhaps in cases in which the mother has a minimal, healed lesion, and it is highly desirable to give the baby a good start in life. In such cases the baby may be nursed for six to eight weeks.

During the first twelve to sixteen weeks of pregnancy, therapeutic abortion is indicated in all proved active cases of pulmonary tuberculosis. This holds true for any stage of pulmonary tuberculosis, early or late.

From the sixteenth to the twenty-eighth week, artificial interruption should rarely be undertaken, except in active cases in which the patients are growing rapidly worse.

From the twenty-eighth to the fortieth week, nothing can be done that will improve the condition. "Watchful waiting" may seem cowardly, but surgical intervention is almost sure to terminate fatally.

If the pregnancy has been carried to or near full term, labor should be made as easy and short as possible. As soon as the cervix is fully dilated rupture of the membranes, if these have not previously ruptured, episiotomy with application of forceps and immediate delivery using gas-oxygen, cyclopropane or local anesthesia during the active delivery is the procedure of choice.

J. P. GREENHILL.

Scadding, J. G.: Pregnancy and Oleothorax, Lancet **1:** 1329, 1938.

The author reports a case of tuberculosis treated by oleothorax because of an adhesive pleuritis developing subsequent to artificial pneumothorax performed four weeks post partum.

The course of a second pregnancy beginning two months following oleothorax was uneventful. There was no significant interference with the intrapleural pressure.

It is suggested that in suitable cases this method of collapse therapy should be considered.

CARL P. HUBER.

White, G. M., and Porter, D. F.: Miliary Tuberculosis in a Newborn Infant, Canad. M. A. J. **39:** 165, 1938.

The authors report the case of an infant who died of miliary tuberculosis on the forty-sixth day of life. Evidence of the infection was noted during the first week of life. No postnatal contact could be determined though all those in contact with the infant were investigated clinically and roentgenologically. The father showed no evidence of tuberculosis. The mother showed evidence of a childhood tuberculosis without activity and a normal course ante partum and post partum. The possibility of placental transmission of the disease during the last weeks of gestation is discussed. The placenta was not examined.

CARL P. HUBER.

Zakon, S. J.: Prenatal Syphilis a Preventable Disease, Illinois M. J. **71:** 438, 1937.

The author states that every woman who has syphilis is in a contagious and infectious stage throughout her childbearing period, regardless of the fact that clinically the case may be classified as latent. The transmission of syphilis from the mother to the fetus takes place about the fourth month of pregnancy. Pregnancy occurring during late syphilis may or may not terminate with fetal infection. The prevention of prenatal syphilis is simple, and under favorable conditions almost certain. Zakon urges early prenatal care with serologic tests regardless of the social status of the expectant mother. Bismuth is used exclusively in the treatment of syphilis during the period of gestation. In a series of 116 carefully followed-up patients who were treated during pregnancy, 107 children were born serologically negative. Nine children were born serologically positive to 9 mothers receiving antisyphilitic treatment, but only one as early as the fourth month of pregnancy.

EUGENE AUER.

Smyth, Francis Scott, and Olney, Mary B.: Diabetes and Pregnancy, J. Pediat. **13:** 772, 1938.

Personal studies together with critical consideration of the literature lead the writers to conclude that under rigid control, pregnancy in a diabetic woman may take a satisfactory course and yield a normal child. It is difficult to prove that the infantile insulin production has any effect on the maternal blood sugar. When the maternal diabetes has not been adequately controlled, the newborn infant may present temporary symptoms referable to hypoglycemia, which may persist up to three weeks and may require parenteral glucose administration. In some instances the hypoglycemia seemed to be correlated to a hypertrophy or hyperplasia of the Langerhans Islets as ascertained at necropsy. Relative macrosomia, advanced bone age, and a more mature genital tract suggest a pituitary effect. With further advance of information on endocrine relationships, it might become possible to account for mild as well as the fatal hypoglycemia of the newborn. Fetal glycogen storage hypertrophy is postulated by the writers as possible etiology for some of the pathology found post mortem.

HUGO EHRENFEST.

Hector, A. G., and Giove, J. L.: Spontaneous Glycosuria During Pregnancy and the Puerperium, Bol. Soc. chilena de obst. y ginec. **3:** 367, 1938.

From an extensive study the authors conclude that glycosuria is not very frequent in pregnancy. It was found in only 2.85 per cent of the cases observed, occurring generally in the middle third of pregnancy. It was present more frequently in multiparas than in primiparas. A low renal threshold for glucose appears with pregnancy and disappears with parturition.

Lactosuria during pregnancy is very rare and occasionally may follow glycosuria but is absolutely independent. Lactosuria in the puerperium is more frequent. The authors found it in 69 out of 100 cases. It is very transitory, disappearing usually from ten to twelve days after the child is born.

MARIO A. CASTALLO.

Gray, C. H.: Ketonemia in Diabetes and Pregnancy, Lancet **2:** 665, 1938.

In the diabetic patient a close agreement was found between the degree of ketonemia and ketonuria as well as with the clinical condition. In pregnancy 1 per cent of 3,000 patients showed a positive Rothera test for ketone bodies in the urine. Blood ketones varied within normal limits even in 5 cases of eclampsia. There is a greater lability to ketosis in pregnancy as shown by 17 positive Rothera tests in 27 pregnant patients following a fourteen-hour fast as compared with no positive tests in 27 nonpregnant patients.

CARL P. HUBER.

Mortara, F.: Experimental Research on the Functional Alteration in the Number of Functioning Glomeruli During Pregnancy, Monit. Ostet. ginec. **8:** 487, 1936.

From experimental studies on laboratory animals the author came to the conclusion that the number of functioning glomeruli ordinarily represent 38 per cent of the kidney substance, but that during pregnancy this amount is increased to between 55 per cent and 60 per cent.

MARIO A. CASTALLO.

Tamburell, G.: An Unusual Case of Hematuria in Pregnancy, Trans. Sicilian Soc. Gynec. & Obst., Meeting of May 14, 1937.

The author describes a case of bilateral renal hematuria recurring in five pregnancies. After having excluded, by history, clinical and laboratory examination, the possibility of a previous kidney disease, tubercular lesion, calculi, renal ptosis,

and also the pressure caused by the gravid uterus, the author believes that the hematuria was either the result of a toxic factor of pregnancy or due to a dilating effect of pregnancy hormones on the renal capillaries.

AUGUST F. DARO.

Turley, H. K.: Management of Pyelitis of Pregnancy, South. M. J. 31: 729, 1938.

The mechanical obstruction of the ureter at the pelvic brim by the enlarging uterus with subsequent proximal dilatation and stasis, producing what has been termed a "physiologic hydronephrosis," is generally accepted as the causal factor. The condition occurs with greater frequency on the right side, and usually makes its clinical appearance about the sixth month, although ureteral dilatation begins early in gestation. Stasis in the urinary tract favors infection. Distant foci may be predisposing factors, and the route of infection may be either by the lymphatics or the blood stream. The organisms most frequently present are *B. coli,* staphylococci and streptococci. Intravenous urography is a most useful method of investigating the presence of urinary tract anomalies, the size and position of the kidney and ureters.

Pyelitis in early pregnancy can be cured. In the latter half of gestation only control of the infection may be expected. Urologic investigation should be performed when pyelitis develops in the first trimester before the uterus has attained sufficient size to cause obstruction, in order to rule out the presence of anomalies that may have antedated the gestation. In acute cases fluids should be forced and the patient alkalinized. Should no improvement occur in 24 to 36 hours, ureteral catheterization is indicated with fluid administration by intravenous route (3,000 to 4,000 c.c. of 5 per cent glucose) and by mouth. When the temperature is normal the catheters should be removed and urinary antiseptics or acidifying agents given. Methenamine, ammonium chloride and mandelic acid are useful preparations, A ketogenic diet is contraindicated. One should watch for symptoms of acidosis. Lavage of the renal pelvis at ten-day intervals is indicated upon failure of response to the urinary antiseptics or the acidifying agents.

After the fifth month of pregnancy treatment should be directed toward controlling the infection until after the delivery, rather than an attempt at a cure. Resort may be had to ureteral catheterization in patients with chills, fever and sweats who have not responded to the more conservative regime of diuresis and alkalinization. Since ureteral catheters are of value only while they are in place, and should be left in situ not more than 36 to 72 hours, it is advisable to employ postural drainage. With the patient in dorsal position, and the foot of the bed elevated 12 to 14 inches, there is an upward displacement of the kidney which tends to stretch kinked ureters and effects some release of uterine pressure on the ureters at the pelvic brim. When pain and toxic symptoms have disappeared, the patient is advised to rest two hours daily in this position and sleep at night with the foot end of the bed raised.

The severe secondary anemias which tend to develop in severe febrile attacks of pyelitis should be watched for and treated by blood transfusions.

Where response to treatment fails, and there is no abatement of toxic symptoms, interruption of pregnancy is advised. Kidney surgery carries great risk and is rarely indicated.

ARNOLD GOLDBERGER.

Gibson, A. J.: Twin Pregnancy Complicated by Bilateral Hydronephrosis, Med. J. Australia **1**: 472, 1937.

Because of hematuria, frequency of urination, headaches, edema, and slight albuminuria developing at the thirty-sixth week of gestation in a 29-year-old multipara with twin pregnancy, an intravenous pyelogram was done to rule out gross renal abnormality. An advanced degree of bilateral hydronephrosis was detected.

Normal spontaneous birth of twins occurred three weeks before term. Approximately two months post partum the pyelogram was repeated and revealed persisting, definite bilateral dilatation of the calyces and ureters with no evidence of hydronephrosis; kidney function fairly satisfactory.

Dilatation of the upper urinary tract which occurs in nearly every pregnant patient is more marked in primigravidas than in multiparas, developing as early as the tenth week. It is at first uniform bilaterally, but by the end of the fourth month becomes greater on the right side because of uterine pressure. Stasis, which is usually coexistent with dilatation, begins early in gestation and becomes maximal at the sixth month, decreasing near term.

The fact that the ureteral dilatation that occurs with large ovarian cysts not associated with pregnancy is much less than that developing in pregnancy, is evidence that a causal factor exists other than pressure alone. The author suggests that the tone of the urinary tract may be influenced by variations in estrin content of the blood during gestation and the puerperium in much the same manner that uterine tonus is affected.

ARNOLD GOLDBERGER.

McGowan, J. M., and Baker, J. O.: The Relation of Pregnancy to Biliary Disease and the Control of the Vomiting of Pregnancy, Canad. M. A. J. **39:** 133, 1938.

The authors believe that spasm of the second portion of the duodenum is responsible for the production of vomiting in pregnancy. Such duodenal spasm may be produced in the normal individual by the subcutaneous injection of morphine gr. ⅙. It is relieved by inhalation of amyl nitrite and particularly by the sublingual administration of glyceryl trinitrate (nitroglycerin).

X-ray studies of the duodenum in a case of hyperemesis gravidarum demonstrate the duodenal spasm.

Glyceryl trinitrate, gr. 1/100 under the tongue after each meal, has given good results in the control of early cases of vomiting of pregnancy. Five patients successfully treated in this way had not responded to other methods.

CARL P. HUBER.

Kent, C.: Fourteen Personal Cases of Acute Yellow Atrophy of the Liver, Zentralbl. f. Gynäk. **62:** 429, 1938.

The author observed an epidemic of 14 cases of acute yellow atrophy of the liver in Istanbul. Only one patient survived. All the patients were pregnant, all but one were multiparas and all were between 17 and 33 years of age. The early symptoms were not characteristic but appeared to be those of an intestinal intoxication and not those of hyperemesis or a toxemia. In all cases, the liver was found to be diminished in size clinically. In some cases it was reduced to one-third its normal size. Contrary to the belief of older authors, in not a single instance was the so-called pathognomonic presence of leucin and tyrosin crystals detected. All of the patients aborted.

The author emphasizes that there is a vast difference between acute yellow atrophy and the toxemias of pregnancy. The toxemias of pregnancy, hyperemesis and eclampsia affect chiefly primiparas whereas acute yellow atrophy is observed most often in multiparas. Furthermore, in most cases of toxemia the disease disappears after termination of the pregnancy whereas in acute yellow atrophy neither spontaneous expulsion of the fetus nor artificial interruption of the pregnancy has the least effect on the course of the disease. Death of the fetus in utero is unusual in eclampsia but is the rule in acute yellow atrophy.

The Istanbul epidemic of acute yellow atrophy is a unicum in the history of this disease because ordinarily it is a very rare occurrence.

J. P. GREENHILL.

Garcia, Eusebio Y.: Can Malaria Be Contracted in Utero? J. Philippine Islands M. A. **18:** 141, 1938.

The author reports two cases of possible congenital malarial infection with the finding of parasites in the cord in both, and in the internal organs of one of the fetuses whose mother died of cerebral malaria due to *P. falciparum*. He feels that in these two cases he furnished more positive evidence for the possibility of congenital infection with malaria than has so far been recorded in literature by other authors. The possible mechanism of the invasion of the fetal circulation by the parasites from the maternal side is described.

C. O. MALAND.

Hildebrandt, Alwin, and Otto, Hans: Polyneuritis of Pregnancy and Its Response to Vitamin B_1, München. med. Wchnschr. **85:** 1619, 1938.

The authors report the case of a pregnant patient who was severely afflicted with a polyneuritis and to whom was given a total of 1782 mg. of vitamin B_1 besides other vitamins, during the entire period of pregnancy, with no untoward symptoms of overdosage or of any cumulative effects. A healthy child was normally born and the polyneuritis was cured. A number of laboratory studies showed that until shortly before delivery no vitamin B_1 was excreted and vitamin C in only a small quantity; but at the time of and after delivery a normal output was observed in the urine and vitamin B_1 could be found in the serum. Along with the improvement of the polyneuritis under the treatment with vitamin B_1, the subacidity of the gastric juice became normal, and the existing hypochromic anemia was cured, the blood sugar was slightly affected (temporarily lowered), and an existing liver disturbance was adjusted. Before any interruption of pregnancy is undertaken, despite the severe symptoms of paralysis, a trial with vitamin B_1 is advisable.

C. E. PROSHEK.

(To be continued.)

Item

American Board of Obstetrics and Gynecology

The next written examination and review of case histories (Part I) for Group B candidates will be held in various cities of the United States and Canada on Saturday, January 6, 1940, at 2:00 P.M. The Board announces that it will hold only one Group B, Part I, examination this year prior to the final general examination (Part II), instead of two as in former years. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held in June, 1940.

Applications for admission to Group B, Part I, examinations must be on file in the Secretary's office not later than October 4, 1939.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting in Atlantic City, N. J., on June 8, 9, 10, and 11, 1940, immediately prior to the annual meeting of the American Medical Association in New York City.

Applications for admission to Group A, Part II examinations must be on file in the Secretary's office not later than March 15, 1940.

After January 1, 1942, there will be only one classification of candidates, and all will be required to take the Part I examinations (written paper and case records) and the Part II examinations (pathological and oral).

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.